

Clinical research in minors and the mentally ill

Felix Thiele, Jörg M. Fegert, Günter Stock (eds)



EUROPÄISCHE AKADEMIE

zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen
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Foreword

Research in vulnerable populations, especially in minors and in the mentally ill, is becoming an increasing and urgent problem. For example, a large part of pharmaceuticals which is given to minors and adolescents is not licensed for them; whereas in other cases effective pharmaceuticals have not been developed yet (e.g. dementia). Recently, politicians have taken steps to remedy this deplorable state – e.g. by introducing the regulation (EC) No 1901/2006 on medicinal products for paediatric use. The realisation of this regulation, however, is causing a number of ethical, legal and economical problems: It is debated, to begin with, to what extent and on which ethical and legal foundation risky research in vulnerable populations is acceptable at all. In addition, the realisation of clinical studies in smaller groups of patients (infants, minors, adolescents) is complex, time-consuming, and therefore very costly. Thus, the question arises whether the established ways of drug development are appropriate at all for fulfilling societal needs.

The present volume is based on the talks given by an international panel of experts covering the fields of paediatrics, psychiatry, pharmacology, ethics, and law during the conference “Clinical Research in Vulnerable Populations” jointly organised by the Berlin-Brandenburgische Akademie der Wissenschaften, the Klinik für Kinder- und Jugendpsychiatrie/Psychotherapie Universitätsklinikum Ulm and the Europäische Akademie GmbH in Berlin in April 2008.

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Contents

Clinical research in the mentally ill. Ethical considerations	
Hanfried Helmchen	7
The ethics of psychopharmacological research in legal minors	
Jacinta O. A. Tan, Michael Kölch	33
Clinical Research in Vulnerable Populations. The Legal Framework	
Gerfried Fischer	63
Regulation (EC) No 1901/2006 on Medicinal Products for Paediatric Use & Clinical Research in Vulnerable Populations	
Birka Lehmann	77
Recent Developments and Strategies in Pediatric Pharmacology Research	
Benedetto Vitiello	91
Pharmaceutical research in paediatric populations and the new EU Paediatric Legislation. An industry perspective	
Philippe Auby	101

Clinical research in the mentally ill.

Ethical considerations

Hanfried Helmchen

Summary

The review deals with present problems i) of protecting mentally ill patients who are incompetent to give informed consent to participating in clinical research, and ii) of assessment of the capacity to consent.

1. Clinical trials of drugs on efficacy and safety in incompetent patients are ethically justified and legally admissible if the investigational drug can be expected to exert a direct potential individual benefit and if such trials will be performed under defined criteria to protect these vulnerable patients. In Germany it is questionable how far these prescriptions of the German Drug Law (Arzneimittelgesetz, AMG) are transferrable to other than drug research.
2. Research with no direct potential individual benefit or only a group-specific benefit in incompetent patients is controversially discussed. However, it may be ethically justified as an exception, and is in Germany legally admissible only in minors, but not in adults.
3. However, internationally there exists a wide range of legal regulations, terms, interpretations, and practices of research with vulnerable persons (Helmchen 2002). In the past years a shift seems to have developed from normatively oriented discussions to more empirically based investigations. Especially vague but clinically relevant terms in protection declarations or guidelines have been better specified, put in concrete form by anchor examples, and empirically studied.
4. In general the criteria of protecting the dignity and, even if impaired, the autonomy of incompetent patients as subjects for research appear to guarantee a high standard of protection. However, the application of these criteria must be improved by practicable procedures. This is valid particularly for the assessment of the basic criterion whether a patient is capable of consenting or not.
5. Open Questions are formulated as need of research.

The basic problem

Mental disorders may impair the basic prerequisite of research with humans: the capacity to give informed consent to participation in research projects. Therefore, clinical research in patients with mental disorders poses two major problems¹:

1. protection of incompetent² patients;
2. assessment of the capacity to consent.

1. Protection of incompetent patients

The public debate on research with vulnerable people was dominated by the concern of violating human dignity and autonomy through instrumentalising incompetent mentally ill people by research, people who are viewed as vulnerable due to their incapacity to defend their rights for themselves³. However, there are also reasons for research in such patients, particularly those with new morbid states such as apallic syndromes or with an increasing quantity of states such as emergencies in need of intensive care or demented patients⁴. These reasons result from adherence to the principles of welfare by developing or optimising therapies as

¹ My considerations are based on i) my 2002 comparison of legal regulations of research with incompetent adults in 30 countries worldwide (Helmchen 2002), ii) my 2003 statement on research in incompetent patients for a hearing of the German Federal Parliament („Bundestag“) (Helmchen 2003), iii) my 2005 short summary of the development of the problem from 1990 up to 2005 (Helmchen 1990; Helmchen 2005), iv) a systematic pubmed search and evaluation of the scientific literature of the last three years (2005–2007/8) including recent analyses and reviews (2007; Petrila 2006; Saks and Jeste 2006; Vollmann and Winau 1996).

² In the following the term “incompetent” explicitly does not mean handicapped but has the specific meaning of incompetence to give informed consent.

³ A positive definition of vulnerability as “unconditional obligation of rescue with the best possible methods” is an exemption in the literature (Rittner 2007).

Protection of vulnerable persons needs special attention. One subgroup of such persons are patients without the competence to give informed consent. Their protection is relevant to all medical interventions, but – due to the intended benefit not only for the individual patient him/herself but mainly for others – particularly in research projects. The historical background for the refusal of research with incompetent patients were – from the present day’s view – unethical or even criminal research investigations. In Germany they led as early as in 1900 as well as once more in 1931 to regulations and guidelines and especially, in 1947, to the Nuremberg Code; they all declared the principle of voluntary and autonomous consent of a competent person as a basic precondition for participating in a research project (Vollmann and Winau 1996).

⁴ Demographic change with a steep increase in the numbers of old people and the frequency particularly of dementia were major reasons to discuss the inherent ethical problems of research with such vulnerable patients, beginning in the 1980’s, and to develop rules to deal with these problems (Helmchen et al. 1989; Hodge 1989; Kendell 1989; Langley 1989; Levine 1986).

well as not harming patients by unproven measures, i.e. by non-evidence-based treatments (Rittner 2007). Therefore, in any case every medical consideration of research with such incompetent patients is imperatively interwoven with ethical questions. In the following I will deal with some major proposals for solving this dilemma.

Proposals of protective criteria and procedures. A first step was done by the Declaration of Helsinki, the leading guideline for medical research since 1964, which included (now in § 24) the possibility of research with incompetent patients under the conditions that

- “a legally authorised representative” has given informed consent,
- “the research is necessary to promote the health of the population represented” and
- “this research cannot instead be performed on legally competent persons”.

A later revision added (by § 26) even the possibility to include patients without consent, “including proxy or advance consent”, but indeed “only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population”.

In the nineties in Germany some expert bodies⁵ developed specific rules for research with patients without the capacity to consent. The 1995 proposals of a group of psychiatrists and lawyers (Helmchen and Lauter 1995) triggered the 1997 statement of the Central Ethics Committee at the Federal Chamber of Physicians on “the protection of patients without competence to consent in research” (Zentrale Ethikkommission bei der Bundesärztekammer 1997).

This statement divided research among four different groups of incompetent patients:

1. Medically indicated but experimental treatments with a *direct* potential individual benefit for the participating patients themselves, i.e. single case trials (“Heilversuche”) or clinical trials (at best as controlled clinical trials) with defined groups of patients.

⁵ Arbeitskreis “Forschungsbedarf und Einwilligungsproblematik bei psychisch Kranken“ (Helmchen and Lauter 1995); Arbeitskreis medizinischer Ethikkommissionen (DÄ 1996, C 2209); Kommission für Ethik in der ärztlichen Forschung der Philipps-Universität Marburg (Freund and Heubel 1997).

Example: the application of a new investigational drug with antidementive effects that is expected to reduce symptoms more rapidly, more intensely, more specifically, or with fewer unwanted effects than licensed antidementia drugs.⁶

2. Research with at least a *future* potential individual benefit for the participating patients, i.e. benefit for the further course or later relapses of the disease.

Example: the discovery of pathogenetic factors as a basis for the development of therapeutics that, in case of a long course of the disease, may still help the individual research patient, as it was done by search for specific immune factors in the development of a vaccination therapy against Alzheimer's dementia (Hock et al. 2002a; Hock et al. 2003).

3. Research with *no* (or at least no direct) potential individual *benefit* of the participating patients but for other patients with the same disease or condition or the same age, i.e. a so-called *group-specific benefit*.

Example: pharmacokinetic investigations in multimorbid and multimedicated dementia patients in order to assess specific alterations of the drug metabolism; it is hoped that the results of such investigations will increase an adequate and safe application of these drugs mainly for the group of future multimorbid dementia patients (Hock 2003). Other examples are diagnostic MR-, PET-, SPECT-Studies (Johnson et al. 2005a; Ridha et al. 2007) or genetic studies (Piccardi 2007) in patients with Alzheimer's disease.

4. Research in incompetent patients outside these defined groups is, of course, unacceptable.

Example: an interventional pharmacokinetic study of a drug that is irrelevant for the therapy of such patients, e.g. demented patients without competence to consent.

Furthermore, the statement added new criteria to the known ones that must be given for a justification of research with patients in groups 2 and 3. Thus, such research is justified only if

1. the research project cannot be performed in patients *with competence* to consent,
2. the research project is expected to result in *essential new knowledge* on assessment, clearing up causes, preventing, or treating a disease,
3. the research project is expected to have an *acceptable risk-benefit-ratio*,
4. a *legal guardian* who has appropriate knowledge of the patient gives informed consent,

⁶ By the way: although up-to-now these antidementive drugs have only low efficiency (Helmchen 2007) they are seen as efficacious enough to doubt a placebo-control in future studies of new antidementive substances (Fisk 2007).

5. the patient does not show *refusing behaviour*,
6. the competent ethics committee gives a *positive vote*.
7. Additionally, in group 3 the research project is expected to have *no more than minimal risks* or burdens.

At the same time also the European Council elaborated and published in 1997 the Convention of Human Rights and Biomedicine (CHRB) which dealt inter alia with this controversial problem by the special conditions of its article 17 for research with patients who are not competent to give informed consent. Particularly paragraph 2 of article 17⁷ triggered a heated public discussion⁸: human rights activists strongly opposed the specified rule that such research should be permissible not only as research with indirect potential individual benefits for the involved patients themselves but – even if under strict limitations and as an exemption – with benefit also or only for other patients with

- the same age, or
 - the same disorder or condition,
- i.e. the so-called group-specific benefit.

By the way I would like to mention that “to balance such antagonisms requires that each position be seriously considered. Furthermore, it requires time. As, for instance, the initially very heated and emotional public controversy at the Convention resulted that Germany has still not signed the CHRB, due to the concern that national standards could be eroded, whereas Great Britain refused to sign because it expected a restriction of the freedom of research. In the meantime, the German discussion has become more factual and more differentiated and it has been shown that some standards of the CHRB are superior to the German ones, and that other stricter German standards can be maintained (§ 27 of the CHRB and Art 34 of the Additional Protocol) (Taupitz 1998). Of course not only ethical but also political considerations have played a role here. Public pressure may have prevented the government from signing the CHRB. A disadvantage of this is that Germany, because it is not a signatory power, could not sign the supplementary protocol on banning human cloning although it is strongly in favour of it. Furthermore, Germany is in danger of losing its equally strong voice in the decisional processes of the further development of the CHRB” (Helmchen 2004).

⁷ CHRB, Art 17, 2: “the research has the aim of contributing...to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition” This wide formulation includes research as defined in groups 2 and 3 of the above mentioned CEC-Statement.

⁸ In the nineties especially in Germany a highly emotional one (de Wachter 1997).

In a 2003 hearing of the Ethics committee⁹ of the German Federal Parliament the controversial positions of the acceptability of research with incompetent patients became clear in plain terms again. But a short time ago the Steering Committee on Bioethics of the European Council delivered a Draft Additional Protocol to the Convention, which, by way of exemption, allows group-specific research with no more than minimal risks and burdens (as additional protective criteria to all other criteria mentioned above) (Europarat 2003).¹⁰ Correspondingly, in 2004, the German Central Ethics Committee published a statement on “research in minors” (Zentrale Ethikkommission bei der Bundesärztekammer 2004) and the 12th Revision of the German Drug Law accepted the concept of group-specific benefit for research in minors. In 2006 the working pool of medical ethics committees in Germany¹¹ discussed the European regulation of pharmaceutical research in minors (Klinkhammer 2006). However, the application of the concept of group-specific benefit to adults went on in Germany to be refused or at least considered reluctantly, as, for example, at a public hearing in 2006 of the German National Ethics Counsel, whereas in other countries such as in The Netherlands the law¹² adopted the regulations of Art 17, par 2 of the CHRB (Welie and Berghmans 2006).

The Additional Protocol to the CHRB, published in 2005, dealt with (in § 19) the urgently needed research with incompetent patients in *emergency* cases and asked for determination of the protective criteria by law, in addition to the above-mentioned ones, and for arrangements in case that informed consent cannot be received in time even from an authorised person. In 2007 a proposal of the Ethics Committee of the Physicians’ Board of Rhineland-Palatinate was published for such research (Rittner 2007). This proposal offered a model based on 15 years of successful experience, and discussed extensively the problem of a *deferred* consent. It is to be proven whether this justification of a deferred consent for research with incompetent emergency patients (as well as the § 26 of the Helsinki Declaration mentioned above) is applicable to research with incompetent acutely psychotic patients, e.g. acute episodes of severe mania in which a consent of the legal guardian cannot be received

⁹ Enquête-Kommission Ethik und Recht in der Medizin.

¹⁰ Which was published in 2005 for signing by the European member states. However, the Additional Protocol can be signed only by states who had signed the CHRB itself (Klinkhammer 2006). The Protocol can be downloaded from www.aerzetblatt.de/plus0405.

¹¹ Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland.

¹² Dutch Medical Scientific Research on Human Subjects Act.

in time: although the specific context of the German drug law (Arzneimittelgesetz, AMG) is related to clinical trials of drugs the law speaks only of “treatment”¹³.

Example: in acutely admitted patients with chronic alcoholism videotapes of delirious states were taken in order to show them to the patients after remission as a preventive measure against relapses. With regard to the questionable capacity to consent in these patients the summary statement “all patients and their families signed informed consent” may be misleading. Apart from the fact that a consent of (legally not authorised) proxies appears permissible in Romania but not in Germany, it attracts attention that proxies as well as patients gave their informed consent. The description of the recruitment procedure of patients reveals an explanation insofar as “two patients did not agree to sign the patient informed consent and their videotapes were destroyed”: apparently the informed consent was collected from the patients after remission, i.e. as a deferred consent (Mihai et al. 2007).

Responsibility of the ethics committee. Finally, the protective power of ethics committees will be strengthened.¹⁴ In Germany the change from a purely advisory institution to an official one increased the responsibility of ethics committees with a binding character of its votes – and made them liable to examination by courts of administrative law. The general recommendation of the Additional Protocol (Art 9, par 3) that the ethics committee “shall produce an opinion containing reasons for its conclusion” should be specified in research with incompetent patients insofar as not only negative votes but also positive votes should give reasons. In research with incompetent patients in which only group-specific benefits can be expected, the ethics committee or – as proposed by the above-mentioned proposal from Rhineland-Palatinate – a Data Safety Monitoring Board (DSMB) should monitor independently and continuously the research project and should stop the study if more than minimal risks or burdens appear or if the superiority or inferiority of one of the compared groups (Prüfarm) could be established (Rittner 2007).

Points in need of clarification. Controversial discussions with regard to the *protection criteria* are related to the meaning of terms such as “research” in relation

¹³ AMG § 41 (1) 2: “Kann die Einwilligung wegen einer Notfallsituation nicht eingeholt werden, so darf eine Behandlung, die ohne Aufschub erforderlich ist, um das Leben der betroffenen Person zu retten, ihre Gesundheit wiederherzustellen oder ihr Leiden zu erleichtern, umgehend erfolgen. 3 Die Einwilligung zur weiteren Teilnahme ist einzuholen, sobald dies möglich und zumutbar ist.”

¹⁴ Perhaps it would be better to leave the full responsibility for ethical conduct of research with the researcher, whereas the responsibility of the EC should be to prove the ethical arguments for doing the research and to control its performance.

to “care” and others (see below under “*Explanations*”). Most of these terms are indefinite terms (mainly those of law). It is impossible to make them so explicit that they keep their generality as well as to serve the unequivocal assessment of every individual situation.¹⁵

Moreover, international guidelines such as the Declaration of Helsinki or the European Convention left terms vague in order to make possible an international compromise. However, allowing regional interpretations with regard to the regional acceptance of the terms impedes their standardised international use.¹⁶ Therefore, at least for reasons of international comparisons, harmonisation and standardisation of terms and rules in the major guidelines seem to be desirable.

Example: a comparison of the evaluation strategies of 21 ethics committees in 12 European countries of a descriptive multinational study on treatment with acetylcholinesterase inhibitors in mild or moderately severe Alzheimer’s disease (the ICTUS study) revealed considerable differences. The valuation of the study varied from the judgement that the study was “no experimental study” to the study that it was a phase IV drug trial. The authors concluded “the data suggest that there should be more consensus across the EU about which studies or interventions do and which do not require approval of an ethics committee” (Rikkert et al. 2005). This conclusion reveals also that German rules are more restrictive insofar as such study – as all research with human beings – unequivocally must get a vote from the competent ethics committee.

At least, the EU tries to standardise important terms by illustrating them by anchor examples in the Explanatory Report to the Additional Protocol to the CHRB, e.g. for minimal risks and burdens. Article 17 of the Additional Protocol (p 32) states that minimal risks or burdens result “at the most, in a *very slight* and *temporary* negative impact on the health of the person concerned.” One can generally agree with most of the given anchor examples in the Explanatory Report (Nr. 97, p 33). However, for example, there is some discussion as to whether taking even only a small amount of blood from a peripheral vein – not in an intervention in the framework of care but only for research purposes – is no more than a minimal risk. Or the psychological burden of an MRT may be much more than a minimal

¹⁵ Because these terms also contain normative values, it should be kept in mind that empirical findings cannot overcome normative conventions, in order to avoid a naturalistic fallacy.

¹⁶ Even the adherence to basic rules of the European Convention is not certain, as is shown by the fact that Germany as well as the United Kingdom did not sign the Convention even if with opposite reasons (Helmchen 2004) – although the Convention states that every signatory power is obliged to adhere to the Convention’s rules as a minimum but is allowed to use stronger regulations.

risk in a claustrophobic patient. Thus, Article 17 of the AD states that “in assessing the burden for an individual, a person enjoying the special confidence of the person concerned shall assess the burden where appropriate”.

This last point introduces the role of proxies: on the one hand this is supposed to make the research procedures more transparent and could be understood as a confidence-building measure; on the other hand this procedure asks for the role of proxies in the consent procedure.

Thus, the direction of progress will be to illustrate by anchor examples the meaning, content, and boundaries of important but indefinite terms. Specialty associations (e.g. DGPPN¹⁷, AGNP¹⁸, DGBP¹⁹) are to collect such examples and contribute them to the international discussion. The future will show whether and how far it will be possible to find practicable solutions for both keeping the content of a term or principle and taking into account national or regional special normative features.

Explanations. The fallacies of the ambiguity of some of these indefinite but relevant terms of the protective guidelines will be illustrated by a few examples.

1. *What is the meaning of “research” in relation to “care”?*

Apart from various different definitions of research (Helmchen 2002) it is important to recognise that the borderline between research and care may be blurred, and that a categorical decision implies values: a decision for defining an actual procedure as research increases the level of protection for participating patients.

Example: assessment of lab values in a multimorbid and multimedicated demented patient in order to understand an unexpected deterioration as a possible unwanted drug interaction is an act of care with potential individual benefit. However, systematic (e.g. standardized, prospective) sampling of such lab values in a group of such patients can be viewed as research with only group-specific benefit which requires a vote of the ethics committee.

Clinically more important is a patient’s misconception of research as care, i.e. “to confuse the design and conduct of research with personalised medical care” (Miller and Joffe 2006). This situation was labelled 25 years ago by the term “therapeutic misconception” (TM) (Appelbaum et al. 1982). Recently this con-

¹⁷ Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenkrankheiten.

¹⁸ Arbeitsgemeinschaft für Neuropsychopharmakologie.

¹⁹ Deutsche Gesellschaft für Biologische Psychiatrie.

cept has been controversially discussed. It was suggested that the term TM supports the “assumption that clinical trial participation disadvantages research participants as compared with receiving standard medical care” (Miller and Joffe 2006) as well as the reproach that some of its newer interpretations “exaggerate the distinction between research and treatment” (Kimmelman 2007). But such statements were clearly repudiated by the inventors of the term saying:

Our concerns about TM’s impact on informed consent do not derive from the belief that research subjects have poorer outcomes than persons receiving ordinary clinical care. Rather, we believe that subjects with TM cannot give an adequate informed consent to research participation, which harms their dignitary interests and their abilities to make meaningful decisions. ... In the absence of empirical studies on the steps required to dispel TM and the impact of such procedures on subject recruitment, it is premature to surrender to the belief that TM must be widely tolerated in clinical research. (Appelbaum and Lidz 2008)

An investigation by these latter authors resulted in the conclusion that “subjects often sign consents to participate in clinical trials with only the most modest appreciation of the risks and disadvantages of participation” (Lidz et al. 2004).

2. *What is the meaning of therapeutic” versus “non-therapeutic” research?*

The differentiation of “therapeutic” from “non-therapeutic” or “pure biomedical” research has been widely used, particularly with regard to the level of protection that should be higher in the latter one, or even in order to draw a sharp line between permissible and not permissible research. However, the term “therapeutic” may blur the borderline for the patient and have him understand “therapeutic” research as care, i.e. have him be subject to a therapeutic misconception. Furthermore, “the validity of this distinction is questionable” (Welie and Berghmans 2006).

Example: “a therapeutic research study may prove that the experimental intervention is ineffective, in which case undergoing the experimental condition would be not beneficial to the subjects. Conversely, a non-therapeutic study may be associated with benefits for the subjects, such as more attention from health care workers, etc.” (Welie and Berghmans 2006).

Therefore, it has been proposed to use instead the terms research with or without “potential individual benefit” (Helmchen 1998; Helmchen 2002). After all these terms are definitely more even if not completely unequivocal. Since the objective of research is the gain of knowledge, every research with humans goes beyond the individual benefit and is oriented supraindividually. Insofar in every case the

extent of the individual benefit (“eigennützig”) must be related to the benefit of others (“fremdnützig”). The present potential individual benefit will be the strongest in therapeutic trials (group 1 of the CEC-Statement)²⁰, less in research with future individual benefit (group 2), and at most questionable in research with benefit for the group to which the patient belongs by age or disease. Sometimes group-specific research (group 3) will be distinguished from research with benefit only for others (group 4; exclusively “fremdnützig”).

3. *What is the meaning of “direct” benefit?*

If the term direct is understood as a benefit which is evidently or immediately related to the intervention then the question has to be answered, how intensely and how shortly after the intervention the benefit must become manifest. The emphasis of a benefit as direct can be understood also as a rhetorical reinforcement that the benefit must clearly be visible and unequivocally related to the intervention. However, the term “direct” also points to the possibility of “indirect” benefits. Thus, later benefit after a while could be meant, e.g. a preventive effect of a vaccination, or a therapeutic benefit of research on the conditions of a disease from which a new therapy could be developed.

4. *What is the meaning of an “acceptable” risk-benefit-ratio?*

Usually the term “reasonable” or “appropriate” is understood as a justified relationship between risks and benefits. However, manifestation and intensity of both risks and benefits can be estimated only as probabilities (such as “not to be excluded”, “possible”, “probable”). Moreover, these probabilities may vary considerably among individuals; and these differences are relevant if a risk is defined as “the individual’s every-day life risks”. Accordingly, the estimation of the reasonableness of a risk-benefit-ratio depends upon normative values and conventions.

Example: Thus, in studies with more than minimal risks, as in vaccination studies, the ethics committee has to decide whether the risk-benefit-ratio of such therapeutic research would be ethically acceptable in patients with a presently almost untreatable disease such as Alzheimer’s dementia with a fatal outcome (as it is argued for in oncological trials in patients with final stages of carcinomas) but at liberty to the risk-benefit estimation of the authorised persons.

²⁰ According to the above-mentioned statement of the Central Ethics Committee.

5. *What is the meaning of “essential” new knowledge?*

The interpretation of the term “essential” comprises an “essential extension of the scientific understanding of the disease” in the Explanatory Report (number 87) to the Additional Protocol. The circularity in this interpretation shows the difficulty to give a clear, unequivocal, and practicable definition of the term “essential”. Apart from giving a wide understanding of the field in which “essential” gains of knowledge can be made, including knowledge about the causes, the treatment, and the prevention of a disease, the term “essential” itself remains unclear: is it necessary in order to be “essential” i) to be – in content – not less than a breakthrough as a finding that opens new options for treatment, ii) to be – in time – a breakthrough with an immediate effect or also only with a delayed effect, iii) to be evidence-based and – with regard to formal criteria – at which level at least must the new knowledge be evidence-based?

6. *What is the meaning of “consent”?*

Although this question on the nature of consent will be dealt with in the next chapter, one aspect of its protective function must be mentioned here: a legal requirement for research with incompetent patients is an informed consent by an authorised person. However, no German regulation explicitly provides rules for the appointment of a legal guardian (*Betreuer*) for research purposes only; therefore, at least it remains unclear i) whether a judge will appoint a legal guardian only for a research purpose, especially for research in groups 2 and 3, and moreover, ii) whether German law permits a legal guardian (appointed for other than research reasons) to give such consent, because the legal guardian is obliged only to uphold the welfare and best interest of his patient but participating in research goes beyond the benefit for only the patient himself.

2. **Assessment of the capacity to consent**

The range of the problem. Even if the capacity to consent is impaired particularly frequently in severe mental illness – that segment of mental disorders with a strong need for research in order to improve the deplorable fate of its victims, incapacity to consent can be caused also by a wide range of medical or somatic diseases, disorders and conditions (Palmer et al. 2005; Vollmann

et al. 2003)²¹, and will be impaired transiently or persistently according to the respective disease conditions²². Pars pro toto I mention *emergency* cases such as acute cardio-vascular insults or poisoning or polytraumata or severe brain injuries, e.g. by stroke (especially if causing aphasia), mostly in patients to be treated in intensive care units.

Although states of incompetence are associated with diagnoses in different frequencies: coma > dementia > schizophrenia > depression, and mental disorders > other somatic diseases (Appelbaum 2006; Vollmann et al. 2003), the capacity to consent must be assessed in each individual case because this capacity mainly depends on individual characteristics, the stage and severity of the disease.

Lack of standardised and practicable instruments. In contrast to the logical procedure the historical events developed in a reverse order: first rules of protection of incompetent subjects for research were developed, and then the assessment of competence to consent gained importance in the past few years.²³ The reason was that, from a theoretical point of view, the construct of competence seemed to be clear whereas the protection of human beings in the practice of research has always been a problem because progress in modern medicine is based on research (Helmchen and Winau 1986). However, the more medical research expanded also to include patients with questionable or even no competence to consent the more practical problems of its assessment became evident. An indication of this late development may be that the only corresponding remark in the Additional Protocol of the CHRB can be found in Article 14, paragraph 3: “Where the capacity of the person to give informed consent is in doubt, arrangements shall be in place to verify whether or not the person has such capacity.” The corresponding number 79 of the Explanatory Report states that it is the researcher’s responsibility to report to the ethics committee how he will examine the capacity. But no practica-

²¹ Because the respective problems in minors will be dealt with by other speakers I will confine myself to corresponding questions in adults.

²² “Across diagnoses, cognitive capacity, physical functioning, and a diagnosis of mental illness have the greatest impact on decision-making capacity, with level of education also having an impact.” (Candilis et al. 2007).

²³ DC Marson, a leading author in the special field, added “an enormous intergenerational transfer of wealth” as a reason of “the greatly expanded incidence and importance of capacity assessment of older adults”, e.g. for questioning the capacity to make a valid last will (“Testierfähigkeit”) (Moye and Marson 2007a).

ble test of capacity is available²⁴ and almost no scientific publication gives information how the capacity to consent was assessed. Therefore, a leading author in the field seems to be right when he states: “Assessment of decision-making capacity in older adults is an emerging area of practice and research” and “becomes a distinct field of study” (Moye and Marson 2007a).

The valid assessment of competence to consent is ethically relevant, because an incorrect estimation either leads to an invalid consent and leaves the responsibility for decisions with an incompetent patient or else discriminates against a competent patient. However, the currently used technique is only a more or less rough clinical estimation based on impression. At best the patient will be asked for his *understanding* of the information on the planned research project given to him/her, i.e. to repeat in his own words what will be done (aim, procedure, expected benefits and risks), why will it be done (reasoning), what does it mean for him/her (appreciation). The use of standardised tests such as the McArthur Test Battery is presently time-consuming and its specificity is insufficient (Vollmann et al. 2003; Vollmann et al. 2004). Also the agreement among different treatment decisional capacity assessment instruments is low (Gurrera et al. 2007a). After all at present short instruments for assessing the capacity to consent are under development; needing five minutes for application, they seem to be practicable.²⁵

Consequences. At least two different ways of overcoming the difficulties of competence assessment in research with questionably incompetent patients are being used:

1. lowering the threshold of accepting the given consent as valid;
2. differentiating types of consent according to the specific research project.

Both ways have been proven increasingly by empirical investigations of various elements of the consent procedure.

Ad 1 Lowering the threshold of accepting the given consent as valid. A characteristic of the first way is the general statement in scientific publications that all participants have given (written) informed consent. However, the procedure of assessment of competence is almost never described. Therefore, it remains unclear whether competence to consent was assessed validly. Even recent publications on

²⁴ At least in Germany.

²⁵ University of California San Diego Brief Assessment of Capacity to Consent (UBACC) (Jeste et al. 2007), Capacity to Consent to Treatment Instrument (CCTI) (Okonkwo et al. 2007).

research with dementia patients give as their only specifications “mild or moderate” states of dementia plus sometimes the range of the MMSE-Score, e.g. 16–26 (Hock et al. 2003). However, a “mild or moderate” state of dementia says almost nothing about the capacity to consent of the individual patient, and in patients with scores of the MMSE below 20 the capacity is in doubt (Karlawish et al. 2005) and should be tested specifically. In line with these doubts are the results of specific investigations of the validity of consent.

Example: a standardised²⁶ assessment of the capacity to consent according to different consent standards (from expressing a treatment choice up to clinically relevant standards of appreciation, reasoning, and understanding) revealed that even “patients with mild cognitive impairment (MCI) showed a progressive pattern of capacity compromise (marginally capable and incapable outcomes) related to stringency of consent standard.” Much worse were the results in mild Alzheimer’s disease (Okonkwo et al. 2007).

Such examples let us assume a change of definitions or of thresholds;²⁷ particularly the threshold for the assumption of lack of capacity to consent may be changed: upwards with the result of accepting an only questionable or impaired capacity as a valid one; or by downward change an impairment of capacity may be accepted with the consequence of appointing a legal guardian for a competent person. Such possible changes of thresholds are in need of empirical research.

Example: if all patients of a vaccination study (Hock et al. 2002a; Orgogozo et al. 2003a) against Alzheimer’s disease who gave written consent would have understood the risk of life-threatening inflammation it can be doubted that all of them would have consented to participate. However, it is unclear whether the patients understood the information of this perhaps unknown but not improbable risk²⁸, or resp. whether there was any control that they had understood and appreciated this information. It would be desirable that all such information on the consent process would be published as part of the paper with the results of the research.

And even if probably competent demented patients agreed with what was proposed to them, the interpretation as assent should be made with caution, not the least because some studies have revealed the emotional and social dimension of informed consent (Sugarman et al. 2007), i.e. the patient’s decision may be influenced by the situational context (Hellstrom et al. 2007b).

²⁶ By the Capacity to Consent to Treatment Instrument (CCTI).

²⁷ In the above-mentioned hearing of the Federal Parliament there was a question about the danger that exclusively group-specific research will be declared as a therapeutic trial.

²⁸ The risk of aseptic meningoenophthalitis manifested in 18 of 298 patients, i.e. 6%.

Therefore, it would be more transparent and ethically acceptable if – according to the high standards of competence – possibly or probably incompetent patients would be declared as incompetent and the study would be performed under the protective premises of research with incompetent patients, i.e. to obtain the consent not only – as assent or even only as acquiescence – from the patient but also from an authorised person. However, as mentioned above, at least in Germany this could be difficult because judges could refuse to appoint a legal guardian due to the law that such guardians (*Betreuer*) have only the competence to act exclusively in the best interest of the individual. The simpler but to date scarcely used way is for the competent patient him-/herself to authorise a person of his/her confidence for later decisions with regard to research.

Ad 2 Differentiating types of consent. An alternative way differentiates the consent with regard to i) specifics of the research question and to ii) various consent standards, but asks iii) also for the validity of consent. Empirical findings are:

- i) Consent specificity: Capacity to consent is not an absolute one but only relative to the point in question; it may exist with regard to one topic but not to another one at the same time in the same person. Also it is not a stable feature of a person but may change in time. Therefore, it is crucial to obtain the consent for participation in the actual research project, and it must be valid here and now. And, since mental abilities are not static, “the enhancement of the patient’s capacity is a reasonable aim” (see below). Some authors emphasize the clinical experience that the capacity to consent may be related to specifics of the research project, e.g. treatment of an acute stroke, or elective cataract surgery in demented patients, or in geriatric patients²⁹, or in dementia. It seems to be an interesting idea that demented patients not even capable of giving independent consent themselves may be capable of appointing a proxy of confidence for research consent.³⁰ Cor-

²⁹ “It should neither be assumed that most adults over a certain age are too demented to consent nor that decision-making is approached the same way by younger and older adults” (Gatz 2006).

³⁰ “Laypersons at heightened risk of Alzheimer disease discriminate among research scenarios of varying risks and burdens. They are supportive of surrogate consent-based research even when risks and burdens are significant to the subjects; these opinions appear to be based in part on their assessment of risks as well as on their general attitude toward biomedical research.” Kim et al. proposed “a rationale for assessing the capacity to appoint a proxy and then described a novel interview instrument for assessing the capacity to appoint a proxy for research consent.” (Kim and Appelbaum 2006)

respondingly it was found that lay persons at risk of dementia support surrogate consent to research (Kim et al. 2005).

- ii) Consent standards: Analysis of the consent process yielded differences in both the quality and the expression of consent. Major components of consent are evidencing a choice, understanding, reasoning, and appreciating information (Grisso and Appelbaum 1995; Helmchen 1995; Vollmann 2000b). Evidencing a choice is seen as a minor standard whereas understanding represents a major standard, and existence of all of these abilities together is judged as the highest standard. Furthermore, there exists flexible gradation among various forms of evidencing a choice, mainly consent as an informed autonomous decision, assent as adherence to a proposal, acquiescence as a tacit agreement, or even no refusal.

Application of the highest standard of consent would eliminate a major part of the mentally ill as potential probands as well as many potential probands with other medical diseases and even some healthy persons, or would require a legal guardian for them to consent to research. Therefore, it should be asked which standard of evidencing a choice will be appropriate, e.g. with regard to the risk-benefit-ratio of a research project. Lower standards of consent are presumably implicitly and frequently used in clinical practice. However, ethically it would be preferable to determine explicitly in each research project which standard of consent will be ethically acceptable, e.g. a lower standard in only minimal risk-studies.

- iii) Consent validity: All sources of consent, the patient himself, his/her advance directive, and authorised persons, may be flawed.

Example: In an interview-study of competent patients and patient-identified surrogate decision makers with scenarios of current state of mental health and progressive dementia patients' preferences regarding elective cataract surgery, the choices were predicted correctly by surrogate decision makers only in the state of mental health but not in the hypothetical dementia scenario where "proxies were unable to accurately represent a patient's wishes for elective cataract surgery" (Mantravadi et al. 2007).

Comparing this example with the above mentioned one in which lay people with an increased risk of dementia supported the consent to participate in research by surrogates (Kim et al. 005) it may be asked how validly such investigations may represent real situations.

Measures to improve the validity of consent. To comply with the high standard of full capacity to consent, various procedures have been investigated either i) to

improve an impaired capacity, or ii) to substitute it by an advance directive, or iii) to substitute it by the valid consent of a proxy.

- i) Enhancing the patient's capacity to consent: "Persons with cognitive dysfunction are commonly excluded from making decisions about the implementation of cognition-enhancing treatments although they wish to do so" (Ritchie and Portet 2006). Various procedures of enhancing the capacity to consent had been proven as efficacious (Flory and Emanuel 2004a) not only in schizophrenia (Appelbaum 2006; Carpenter et al. 2000) but also in dementia (Mittal et al. 2007). Thus, e.g. the procedure of "experienced consent", i.e. experiencing research by participation in a try-out of one week, is seen as promising (Welie and Berghmans 2006). However, a systematic review of 42 trials yielded "only limited success. Having a study team member or a neutral educator spend more time talking one-to-one to study participants appears the most effective available way of improving research participants' understanding; however; further research is needed" (Flory and Emanuel 2004a). One study found that context cognitive training "improved cognitive abilities specific to the abilities trained and continued five years after the initiation of the intervention" (Willis et al. 2006).
- ii) Advance directives: Advance directives with regard to research are feasible but perhaps do not assist the patient's or proxy's consent decisions (Stocking et al. 2007). They are – to my knowledge – scarcely used but recommended (Korczyn 2007). Consequently, "three major international documents on medical research – the CHRB (ETS 164), its Additional Protocol (ETS 195), and Directive 2001/20/EC on Clinical Trials on Medicinal Products – give conflicting messages on the legal status of advance directives in medical research" (Lötjönen 2006).
- iii) Educating authorised persons³¹: Clinical-scientists "must be prepared to educate patients and family members about dementia and research, determine each potential subject's competence to consent, and ensure that decisions about participation are in accordance with the best interests of the subject. Ethical conduct of clinical trials of new antidementia therapies which will require that everyone involved understands the values and beliefs that guide their decision-making and the potentially conflicting roles facing the clinician-scientist" (Fisk 2007).

³¹ Next of kin, authorised proxies, legal guardians.

This is important because “...proxies ... themselves have biases about their loved ones and their potential for participating in research” (Beattie 2007), and there seems to be “poor agreement between the decisions made by surrogates and patients.” ”Surrogates’ decisions would have resulted in the patients having far more treatment than the patients would have wanted.” “Further study is needed on measures such as facilitated discussions, advance directives and the difficulties that surrogates face, in order to improve the accuracy of surrogates’ decisions and respect of patients’ autonomy” (Li et al. 2007).

The role of spouses of persons with dementia as potentially responsible gatekeepers for excluding people with dementia from participating in research needs further consideration, “with particular reference to the appropriateness of viewing consent as a primarily cognitive, universalistic and exclusionary event as opposed to a more particularistic, inclusive and context relevant process” (Hellstrom et al. 2007b).

In addition it should be mentioned that interviews of caregivers about ethical concerns of drug treatment in dementia patients showed that “problematic consequences of an early diagnosis and the creation of unreasonable hope did not appear” and “problems concerning rising awareness of cognitive decline were not found” (Huizing et al. 2006).

All of these measures yielded conflicting results and are in need of further empirical as well as theoretical research. However, one consequence is clear: the implementation of each of these measures needs time on the part of personnel.

3 Open questions as need for research

The described problems may be summarized as open questions which can be formulated as needs of research. There is a need

1. to make more practicable the necessarily indefinite terms of the protection criteria in the major guidelines by a comprehensive list of anchor examples;
2. to find a both practicable and ethically acceptable path between the pseudovalidity³² of a questionable informed consent in vulnerable patients, i.e. in those with a possibly impaired capacity to consent, and the – at least in Germany – difficul-

³² I.e., to accept an assent or even a non-refusal of a patient with an unproven questionable capacity of consent as a valid consent.

- ties of appointing legal guardians with the competence to give informed consent for research in concerned incompetent patients;
3. to gather more empirical data on the validity of consent of patients as well as of authorised persons;
 4. to improve methods of assessing the capacity to consent, particularly by the development of brief and sensitive test instruments; such research has to include necessarily incompetent persons, as has been discussed extensively in the literature (Vollmann et al. 2004; Vollmann and Winau 1996);
 5. to analyse the possibilities of specified and graduated consent;
 6. to investigate procedures of calling in proxies to accompany vulnerable patients participating in research for improving transparency and as a confidence-building measure.
 7. With regard to pharmacological research in mentally ill patients without full capacity to consent there is a need to answer the following questions:
which *secondary* investigations beyond the assessment of efficacy and safety are legally acceptable and ethically justified, e.g.
 - i) *pharmacokinetic* (or pharmacodynamic) investigations in multimorbid geriatric or demented patients with altered metabolism and unknown interactions in multimедication as well (group 2 or 3 of the CEC-Statement), or
 - ii) *longitudinal* investigations of clinically (e.g. by psychopathological tests) or interventionally (e.g. by blood taking) assessed variables after vaccination trials that have been stopped due to severe side effects (Hock et al. 2003).

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The ethics of psychopharmacological research in legal minors

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“It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.”
(World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects)

Abstract

Research in psychopharmacology for children and adolescents is fraught with ethical problems and tensions, which has practical consequences as it leads to a paucity of the research that is essential to support the treatment of this vulnerable group. In this paper, we will discuss some of the ethical issues which are relevant such research, and explore their implications for both research and standard care. We suggest that finding a way forward requires a willingness to acknowledge and discuss the inherent conflicts between the ethical principles involved. Furthermore, in order to facilitate more, ethically sound psychopharmacology research in children and adolescents, we suggest more ethical analysis, empirical ethics research and built in ethics input in psychopharmacological research design.

Ethics is an important issue in psychopharmacological research, especially for research amongst vulnerable patient populations. Research involving legal minors is often difficult because of the complexities of consent from legal minors and the emphasis on the protection of children and adolescents. The research into pharmacological treatments for children and young people with mental disorders is particularly fraught, because of the ethical issues surrounding research in what is in effect a doubly vulnerable group of individuals. Unfortunately, these difficulties often become barriers to conducting research with this group and pharmaceutical companies may prefer not to fund such research, giving rise to the current paucity of good research evidence. However, the lack of a good evidence base upon which to treat this vulnerable group is itself ethically reprehensible.

In this paper, we will briefly look in turn at the background of ethics of research and each of several arenas of ethical dilemmas for psychopharmacology research

in children and young people: the premise of research, consent, dilemmas of inequalities of healthcare provision, the impact of research design and the requirement for ‘minimal risk’ and ‘benefit’, and influences of commercial interests. We will suggest that the way forward is to face squarely the reasons for the restrictions placed on psychopharmacological research in minors and the inherent ethical tensions and contradictions, to consider all the ethical issues. This, together with a greater integration of ethical analysis and research into psychopharmacological research methodology, can provide a way forward that enables good, ethically sound research to take place.

The relevance and legacy of history

Medical research has uniquely stringent oversight, and whereas many other disciplines such as sociology and psychology have previously been largely self-regulated with respect to ethics oversight, in the latter half of the 20th century medical research developed a strict, formal and often restrictive system of ethics critique, review and monitoring. This is because of a dark history of abuse by physicians of large numbers of vulnerable prisoners and ethnic minorities in the name of (often scientifically highly dubious) medical research. As a response to these past abuses, and the recognition of the power that those in the medical profession in particular have over patients, ethical codes and principles governing medical research have been developed as early as 1964 when the Declaration of Helsinki was made.

Since then, strict rules for medical research with human subjects have been developed from these ethical principles in most jurisdictions. Medical researchers are legally obliged to abide by these rules. These rules are particularly strict for researchers conducting research amongst patient populations which are vulnerable, for example prisoners, legal minors, the distressed, the mentally disordered, and those who lack competence to give consent. While salutary, it should be borne in mind that this grim legacy has unfortunately sometimes imbued the system with a default assumption that medical researchers are capable of great harm, and must be scrutinised lest they inflict damage on their patients, who as vulnerable individuals must be protected from any harm. This assumption has not been seen in other fields of research such as sociology and psychology. In these non-medical fields, there are relatively few or no regulatory or legal obligations. This is not

ethically consistent as harms can be visited on a person psychologically as much as physically, and through non-medical research as much as medical research. An example of ethically dubious and psychologically harmful experiments are the social psychology experiments carried out by Milgram in the 1960s in which college students were asked to inflict pain on another individual (Milgram 1963).

The landscape, however, is beginning to change. The convention on Human Rights and Biomedicine of 2004 (which is not ratified in all European countries) defines “intervention” in a sense which also includes non-pharmaceutical and non-medical research. Its definition is: “(i) a physical intervention (ii) any other intervention in so far it involves a risk to the psychological health of the person concerned.” (Additional Protocol to the Convention on Human Rights and Biomedicine 2004)

The historical legacy of cruel experiments with vulnerable populations, which is the current high ethical standards and legal requirements on researchers who want to conduct studies with vulnerable populations, has a cruel twist. A paradoxical situation now exists: these populations are now so well protected against research that the standard of routine care is much less well-founded than for the general population as there is less research data available about safety and efficacy of medication and other treatments. In routine care, pharmacological interventions in children and adolescents continue to increase. However, the paucity of available medications specifically licensed for use in this age group, because of the lack of research evidence to support licensing, means that many drugs are used ‘off-label’. ‘Off-label’ use means that they are used outside the bounds of the licence granted to the drug, which specifies the age range, medical indications and dosages for the use of the drug, based on data on efficacy and safety demonstrated by research. ‘Off-label’ use, in contrast, tends to rely on anecdote, personal experience of and confidence in using the drug in question, and consensus amongst colleagues. Benefit-risk evaluations of this ‘off-label’ use are therefore largely missing, with side effects and long-term aspects especially yet unknown (Bakker et al. 2008; Conroy et al. 2000; Horen 2002).

‘Off-label’ use has been recognized as a particular problem for drug safety (Dell et al. 2008; Waller 2007). The rate of ‘off-label’ use is especially high in pre-school children and less so in adolescents, but rates are generally high in comparison with adults (Volkers et al. 2007; Zito et al. 2007). In some countries, ‘off label’

use poses a problem with regard to funding of treatment as health insurers generally refuse to reimburse the costs of using these drugs outside the indications of the licence (Schepker et al. 2007). Another legal and ethical aspect of ‘off-label’ use is who carries the responsibility for liability in the case of side effects or other adverse events (Fegert 2003).

It is an ethical conundrum that the need to protect vulnerable populations against research has the consequence of generating a lower standard of safety in routine care for these very patients, who it could be argued deserve more protection and less exposure to risk in the course of their medical treatment. Research and clinical studies are therefore urgently required in order to reduce the high rate of ‘off-label’ medication use in minors and improve safety (Grieve et al. 2005). These aspects of safety, dosage and the (long term as well as short term) side effects of drugs in children and adolescents – and also the use of these drugs during pregnancy – are frequently discussed, and the consensus is that the state of research at this time is insufficient (Vitiello 2007). At present the state of knowledge on both the safety and efficacy of psychotropic drugs in children and adolescents and the quality of the ethical standards varies according to the age of the patients. Again, there is a paradox that the younger the children, the more limited our knowledge and the more uncertain the benefits and risks of ‘off-label’ use. This is because the younger the age group, the greater the vulnerability and therefore the greater the difficulties of conducting research, and the greater the differences between a child’s physiology and an adult’s and therefore the less the likelihood that adult research results may be informative. Therefore the younger and more vulnerable the child, the less able clinicians are to uphold the ethical standards behind the paradigms of benefiting the patient and doing no harm (Spetie and Arnold 2007).

As these problems have become increasingly recognized over the last decade, the feasibility and efficacy of using legislation to increase the availability of approved and safe drugs for children has been discussed in the USA and Europe. In the USA, special legal regulations have been in existence since the 1990s to encourage the development of paediatric medications by granting further years of patent protection to pharmaceutical companies in return for studies in the paediatric population (Vitiello et al. 2004). This appears to have had the intended effect. Indeed, 11% of all medications with patent protection by the FDA granted for paediatric studies have been neuropharmacological medications. Unfortunately, these regu-

lations have not been without problems (Food & Drug Administration 2003). Several studies on paediatric depression were hurriedly conducted in the USA under the pressure of time before the legislation ran out. As a result, these studies are methodically flawed (Klein 2006). In Europe, similar legislation has been in effect since 2007, but the impact of the ‘EU Regulation on medicinal products for use in children’ has yet to be seen (Kölch 2007).

The underlying premises of medical research

The historical context in which psychopharmacological research in children and adolescents takes place has been important in shaping the dilemmas of the current situation. However, the best way to consider the ethical issues in order to find a way forward is not merely to sketch out the problems as they current exist, but to conduct an analysis of the ethical dilemmas present. The first place to begin the ethical analysis of psychopharmacology research in minors is to lay out the underlying premises of both medical research and the ethical principles that govern its oversight. We would suggest that, when simplified, the ethical reasoning for most interventional research is generally as follows and is represented in most codices concerning research as the Declaration of Helsinki by the World Medical Association or the Belmont Report:

1. The medical profession has a duty to treatment each patient in his or her best interests, by offering the best treatment available and knowing what is the best as well as the safest treatment for the patient’s condition – this is Duty of Care;
2. Research is therefore required to provide the knowledge base in order to fulfil our Duty of Care to our patients;
3. Where possible we should do research without using human subjects but in many cases we do have to use human subjects;
4. If we do research in patients, we should only involve vulnerable patients if there is no alternative group that can be used and the research is necessary;
5. For a vulnerable patient group, protection in their best interests is the rule. Even when such patients give consent or assent, research should only be permitted if it causes minimal harm or distress and has the potential to benefit each patient in the future or others with the same condition;

6. But: Research always has its own risks of harm and research is only justified if there is uncertainty in the outcome, harm or benefit which needs to be determined, which means that there may be as much likelihood of harm or lack of benefit from participation as there is likelihood of benefit;
7. Furthermore, research designs and research physicians are inherently unable to prioritise the interests of the individual participant because their primary objective is to answer a research question and they must follow research protocols;
8. Therefore taking part in research can never really be in the best interests of an individual patient as compared to the best current standard of care.

We therefore come to another paradox – it is clearly in the interests of all patients to have more research take place in order to provide the knowledge to underpin their care, but particularly patients with conditions or in situations which are under-researched; but, it is in theory rarely, if ever, in the interests of an individual patient to take part in research as opposed to getting the best standard of individual care. This paradox means that for an individual patient, the best outcome is achieved by refusing to take part in research but making sure everyone else agrees. This is clearly not feasible, nor is the reality of running trials and taking part in them as clear cut. Nevertheless, it is important to realise that the underlying ethical premise of research participation already contains some inherent internal contradictions.

Living in the real world

There are difficulties with respect to research participation in terms of conflict in ethical principles. The real world is even more complicated, as there are departures in the real world from the assumptions made above. These can broadly be divided into three different categories – constraints due to limitations in access to medical care, constraints due to research design, and constraints due to commercial interests in medical research. Furthermore, the impact of research can be felt not just in terms of the condition and the effects under study. Impact can be found in terms of other aspects of the patient himself, for example his psychological and physical wellbeing; and also his relationships with others and his activities, for example his ability to relate to his family and his ability to learn at school. Therefore any benefit of study may not be limited to the immediate study conditions but

has to be analysed in the context of the environment of the patient. The concept of 'benefit' is problematic, as will be discussed later.

In many real life research situations, some treatments undergoing research would be relatively new and may not be publicly funded nor yet licensed for general use. For some patients, for instance those who have failed to respond to conventional treatment or suffer from disorders with no effective treatment, there may be strong inducement to take part in research in order to gain access to the treatment in question. Balanced against this is the argument that research is inherently more beneficial to the individual in these cases, because without the existence of the research study the patients would simply be denied the possibility of being given those treatments in their standard care.

In some cases where the medication is already in general use, research participation can nevertheless be extremely beneficial to the individual participants. This can happen in a managed healthcare or non-universal healthcare system, where some people may not be able to afford to pay for treatment or may lack accessible medical healthcare resources. This occurs in remote areas in developing countries, and also in industrialised countries in areas of poverty and poorly resourced or unaffordable facilities. Although such patients would not be getting the best possible individualised care by taking part in research, research protocols tend to guarantee good access to high quality care, support and monitoring for all participants at no financial cost to them. Pragmatically, it is certainly more justifiable to allow research participation if this provides better care than participants would otherwise obtain. However, there could be real concern that if the research constitutes the best or, worse, the only recourse to treatment for an individual, whether this constitutes a coercive situation. In such cases, decisions concerning research participation are unlikely to be altruistic in nature but driven by necessity, and such patients may be particularly vulnerable. For example, a participant may not feel able to withdraw from the study because this may compromise his or her care, or he or she may feel obligated to the researcher for his or her help.

Research, therefore, can in reality bring benefits to patients who participate, given the constraints of medical resources many patients experience. That type of situation brings with it the concerns about those patients who are vulnerable because of difficulties in accessing medical treatment having undue inducement and little perceived choice about participating in research in their attempts to seek the optimum

treatment for their conditions. It can also lead to differences in ethical standards required for research in different countries and circumstances – for example, in a developing countries where little medical care is available in remote areas or developed countries where there are areas of poverty and deprivation and no affordable healthcare, any research that would provide medical care for the people living there might be argued to be highly beneficial and therefore ethically permissible, whereas the identical research may not be seen as acceptable nor beneficial in well-resourced areas in developed countries. There is then a danger that countries and neighbourhoods where there are poorer healthcare facilities may be exploited by researchers from richer countries or institutions.

Another aspect of the ‘real world’ of pharmacological research concerns the design of the studies conducted in these vulnerable populations. To improve both the safety of drugs and the quality of research in paediatrics and in child and adolescent psychiatry, it would be essential to consider special needs of children and adolescents and to investigate the effects of combination therapies (psychopharmacotherapy and psychotherapy, treatment with several medications). Unfortunately, this is often not reflected in study designs and therefore the quality of treatment in studies may not represent the state of the art. The exclusion criteria of any additional treatment or severe co-morbidity may simultaneously represent both best practice in terms of protection of the vulnerable and severely ill population and a study design which provides a suboptimal treatment strategy. Furthermore, by failing to represent the real life circumstances of multiple or concurrent treatments, there are risks that research may fail to provide realistic answers that are helpful to clinicians who need to interpret research results and apply them to their clinical practice.

There are other aspects to living in the real world – the nature of other vested interests, such as commercial interests, in pharmacological research. These will be discussed in a later section.

Issues of consent and competence

With regard to legal minors, consent is an area where different ethical principles can conflict:

- The principle of autonomy suggests that individuals who are competent (that is, able to make their own decisions) should generally give consent for their own treatment. There is an ethical obligation to involve all children in decision-making, according to their maturity. In the legal regulations the obligation of parents to involve their children in decision-making is defined in a way similar to the Convention of human rights and biomedicine of the European Council: the will and the mind of the minor “*shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity.*” (Article 6, Convention of Human Rights and Biomedicine)
- The principle of best interests, however, suggests that patients, in particular vulnerable patients, should be protected in their best interests, whatever their treatment decisions are.
- A further principle of protection of children suggests that legal minors are in greater need of protection than other individuals by virtue of their relative immaturity, irrespective of whether they are competent to make their own treatment decisions; therefore they should not be permitted to make major decisions which will seriously harm them.
- There is also a little discussed principle of parental responsibility, which gives parents responsibility for the welfare of their children and therefore a (limited) right to be involved in children’s decisions, where it is relevant and necessary to their role as parents, depending on the child’s state of development and dependency.
- And finally, there is a principle of the importance of family relationships, expressed in the Human Rights Act as ‘a right to family life’, where both children and parents have a right to family life and the relationships involved.

Negotiating the issue of consent involves balancing all these different and often opposing principles. Very young children lack the understanding to make their own decisions, so parents usually make decisions for them, and are expected to do so in their best interests. As children develop, their parents and other adults begin to foster their autonomy, so that they should be increasingly able to make, and allowed to make, more decisions for themselves, in proportion to their maturity and the importance of the decisions. Children’s (and adolescents’) rights with regard to decision-making have to be balanced against their ability to deal with the responsibilities that come with it. Parallel to this, their parents have respon-

sibilities with regard to decision-making inversely proportionate to whether their children are able to make decisions for themselves. These responsibilities endow the parents with rights to information about their children as appropriate to their involvement.

There is a balance between parents or caregivers and minors in the participation of decision-making which varies by age. Whereas in younger children the autonomy of the child may be less developed, autonomy and the right to autonomous decision-making increases with the age as emotional and intellectual maturation occurs. Therefore we can see the autonomy of decision making in minors as a continuum between the extremes of no and of total autonomy of the minor (see Figure 1: Autonomy of minors in decision-making).

Levels of autonomy and participation of minors in decision making

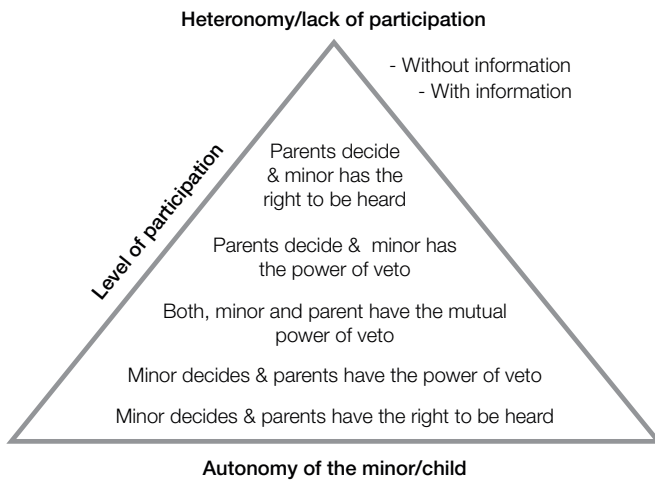


Figure 1: Autonomy of minors in decision making (following Rothärmel et al. 2006)

When children and young people suffer from mental disorders, they become more vulnerable and the issue of protection becomes more important. Because of this vulnerability, the emphasis on protection tends to be greater for research in legal minors, and it is standard for Institutional Research Boards (usually known as

IRBs, which are ethics oversight committees) to insist on informed consent from parents as well as assent or consent from the child or young person for participation in research, which is a higher standard for consent than for treatment. This insistence on parental involvement can be ethically problematic for competent young people who may be taking part in research that involves highly sensitive topics, for example contraception. Even in the mental healthcare setting, there can be issues such as inquiries about concurrent drug use which can become problematic, and logistical difficulties if research is being conducted in certain environments such as schools.

Another area that can be problematic is that of competence. Competence is usually conceptualised as a largely cognitive skill which should be assessed for each specific decision. A person may possess competence to make one sort of decision even if he or she lacks it to make another. There are slightly varying definitions of competence in various legislations and ethical analyses, but in general these include:

- the ability to understand the relevant information;
- the ability to retain the information long enough to arrive at a decision;
- the ability to appreciate its application to oneself;
- the ability to weigh the facts in the balance in order to come to a decision;
- the ability to communicate a choice.

Research has shown that children have the competence to make most treatment decisions by the age of 9 years when given simplified information, and by the age of 14 years when given adult-level information (Billick et al. 1998). This would suggest that even relatively young children should be able to make their own decisions. However, research has also shown that children and adolescents can have other problems with making autonomous decisions (Ondruseket al. 1998). They are more sensitive to the views of the adults around them and susceptible to pressure as well as worries about offending researchers and parents if they change their minds. Having a mental disorder can have an additional impact upon treatment decision-making for children and adolescents. In some cases, they can become more vulnerable and regress in terms of needing more parental support for decisions they may ordinarily be able to make. Having a mental disorder can have complex effects on autonomy. For example, research suggests that having an eat-

ing disorder may distort their sense of identity, values, goals in life and sense of their future (Tan et al. 2003; Tan et al. 2006). Research also suggests that children with attention-deficit/hyperactivity disorder may be influenced by values or hopes of gaining their parents' confidence when deciding whether to participate in a trial which offers them the chance to improve behaviour (Kölch et al. 2008).

Even if they have competence to make decisions, because of their close relationships with their parents, many children and adolescents may prefer to have a group or joint decision-making model, making decisions together with parents and other trusted adults. Children and adolescents who are suffering from mental disorders are probably more likely to prefer, and benefit from, a joint decision-making model (Tan and Fegert 2004).

The concept of benefit

Regulations governing interventional research in vulnerable groups such as children and adolescents generally demand that the intervention should benefit the research participant, and pose either or both minimal risk and minimal burden. Unfortunately, all three of these concepts are problematic both in terms of the underlying ethical issues as well as definition.

The concept of benefit appears to be simple. However, the 'benefit' of a study or of the participation in the study is a measure that resists dichotomisation, so that it can be difficult to be certain whether a person does or does not benefit from research participation. Instead, there is usually a spectrum of magnitudes of potential or actual 'benefit', which can be perceived differently from the points of view of the researcher and the study, and the patient. Furthermore, the measurement of benefit can be difficult, as there are three distinct dimensions on which benefit of participation in a study may be measured. These are the magnitude, the probability and the sustainability of benefit (Raspe et al. 2005).

The first dimension for measuring benefit is the magnitude of the benefit, which depends on the general conditions of the health care system as well as of the disorder and the study interventions. For example, there may be a benefit of being treated as part of research participation in a specialised care unit with very high medical standards, e.g. a University Hospital, with diagnostic examinations and treatments which the patient would never receive if he would not participate in

a study. But in spite of these additional aspects to care he may derive no benefit from the study medication if the study medication does not in fact work for his condition or for him as an individual. The patient may spend more time and effort in having the increased study examinations, which may be seen by him as a burden or disadvantage if he finds them onerous, or alternatively as a positive sign of more comprehensive care and monitoring. These different positive and negative aspects may make it difficult to assess the final magnitude of likely overall benefit obtained from the individual patient having the medication under study.

The second dimension for measuring 'benefit' is the probability of a benefit. How probable will it be that an individual patient will have a benefit of the study intervention? In general this probability may depend on the phase of the study and the state of knowledge surrounding the intervention in question. In determining this, the knowledge about the intervention and the likelihood of benefit to the individual would be greater in Phase IV (post-marketing safety surveillance studies) than in Phase II (drug efficacy) trials. However, the severity or grade of the disease of each individual patient can also affect the probability of benefit from any medication. For example, children with attention-deficit/hyperactivity disorder (also known as ADHD, ADD or hyperkinetic disorder) who have very competent parents possessing high social functioning will probably have a lower probability of benefit of a medication trial as compared to children with less competent parents, but these children with competent parents would also be more likely to respond to parenting skills interventions. In contrast, a child with ADHD and a dysfunctional familiar environment may have a higher probability of benefit, as the parents would have less ability to utilise alternative family interventions. Furthermore, the probability of a benefit of a study may increase with the duration of the study: if a patient is included up to the end of a study there will be a higher probability that he will have a benefit from the intervention and the study-related aspects of care (such as aftercare, follow-ups, etc.). These again may influence the sustainability of the benefits, the third aspect.

The third dimension of sustainability may also be difficult to measure. Sustainability looks beyond short term benefits, e.g. the better care in a specialised unit during the study, and asks whether the interventions and short term effects translate into a longer-term effect. Some interventions may only have a short lived

effect, which requires sufficiently long term follow-up to determine whether and when the effect wears off. Others may have immediate but long-lasting effects, or delayed but longer-lived effects. This is particularly so in children who are still developing and constantly changing. For example, interventions which alter parenting style may not have as marked an immediate effect as medication on psychopathology, but may conceivably have lasting and differing effects over time in terms of a child's behaviour and school performance as well as emotional development.

Benefit, therefore, has to be balanced for a study in general, but also for the single study interventions, the study design and examinations. Benefit has to be further weighed up for each patient in the context of his individual life situation and stage of disease.

The concepts of minimal risk and minimal burden

Because of the emphasis on the protection of children and young people, Institutional Research Boards (IRBs) often insist that many protective mechanisms are built into interventional medicinal trials, and research that involves more than a small amount of risk tends to be rejected. In a recent directive, the European Parliament required that 'minimal risk' should be the standard for trials in children (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001). In this directive, there is a requirement that "medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks". A prerequisite for research is that "some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors". As the directive has to be implemented by members of the European Union in national law, each member state will have to adapt these sentences into its own law.

The definition of this notion of 'minimal risk' is problematic. There are variations in the definition across countries:

- In the United States (The Common Rule, 1991):
“[risks] ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”
- In Canada (2005):
“no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research.”
- In Europe – the Council of Europe (2005) (minimal risk and minimal burden):
“very slight and temporary negative impact on the [person’s] health” and “discomfort [i.e., burden] will be temporary and very slight.”
- In the United Kingdom (2004):
“procedures such as questioning, observing, and measuring children [and] obtaining bodily fluids without invasive intervention; [no] more than a very slight and temporary negative impact on [child’s] health” – Low risk: “might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress; e.g., a blood test.”
- In Germany (German Drug Code: 12. Amendment German Drug Code § 41 (2), 2004):
“If it is expectable that the way of the intervention at best leads to a very slightly and temporarily impairment of the health of the subject. Minimal burden is seen if the intervention causes discomfort which is at the best temporarily and very slightly.”

There is some conceptual confusion around the idea of ‘minimal risk’. Is ‘minimal risk’ supposed to mean ‘minimal distress and suffering’? This interpretation has some merit, as we would wish to inflict minimal pain and distress, irrespective of benefit or risk, particularly for non-consenting individuals such as babies and young children who would have little or no appreciation of the research rationale or benefits. Or is ‘minimal risk’ instead supposed to mean ‘not much greater risk of harm as compared to ordinary life and ordinary treatment’? This alternative interpretation also has merit, particularly when looking at the issue of preserving the best interests of the vulnerable participant. The two definitions would overlap in real life, but are conceptually distinct. For example, a procedure producing a great deal of benefit and relatively little medium to long term harm may be very distressing to an individual. Yet, another procedure exposing an individual to much greater risk of harm than he or she would ordinarily experience may evoke

little distress or suffering. Finally, the standard treatment may cause considerable distress and side effects, and the alternative research treatment may have greater risks in terms of having less benefit and more toxic effects, but be a great deal more pleasant than the currently available treatment.

What are study procedures which can be considered as minimal burden for the patient or have minimal risk for him? Examples that have been given in the regulations for minimal risk and burden are measuring, weighing, and the drawing additional a minimal quantum of blood by an already existing venous access. However, even single and small additional blood drawing may be already a risk which is increased over minimal risk, if the standard treatment has already required a large number of blood drawings or a large volume. Also a repetitive examination which would count in case of a single procedure as a minimal burden may be more than a minimal burden if it is conducted with a high frequency.

The variation between countries about whether they interpret 'minimal risk' to mean lower distress, lower risk, or both, means that there will be ethical confusion about what risk is considered acceptable, and little consistency of the ethical standards adopted by research studies across these countries.

The minimal risk has to be examined in the individual case of each study and indeed each patient. There is no final agreement about the terms and therefore a discussion in study teams and Institutional Research Boards (IRBs) may lead to a different consensus for each individual study. This may disconcert researchers who cannot refer on a standard, but this reflects the general difficulties of applying ethics in research, that general rules are often difficult if not impossible to provide. The researcher himself has the obligation to consider the ethical aspects of the study he plans, and to be prepared to justify his approach. The differences in national guidelines and laws in their definition of minimal risk and burden also requires an individual discussion of study procedures within each jurisdiction to ensure the conformity with national law and its interpretation (Klinkhammer 2006; Wessler 2006).

These stringent requirements concerning minimal risk and minimal burden are clearly designed to protect legal minors who take part in trials. However, once again, the very stringency of these requirements can hinder the conduct of essential research. For example, there are few medical treatments that are proven effective for psychosis in children and adolescents. Good research trials, therefore, would be important. However, the nature of both psychosis itself and the anti-

psychotic medications is such that it would be difficult to ensure that any research participants are only exposed to 'minimal risk'. This may prevent such research, with the result that all children and adolescents are exposed to the even greater risks and distress of having inconsistent and ineffective treatment for psychosis.

Ethical issues in research design

There are two different ways in which research design can be ethically problematic:

1. when the design itself may raise ethical concerns, for example when participants may be at risk or even harmed; and
2. when the design is scientifically sub-optimal, which makes it ethically dubious because we should not subject research participants, particularly those from vulnerable groups, to research which may not be adding good quality evidence to the scientific body of knowledge.

Ethical issues involving research design in the first way include the problem of whether placebos or active drugs are used as the control; and ethical issues involving research in the second are the issue of whether trials have a statistical basis of searching for superiority, equivalence or non-inferiority.

The best design for testing the effect of pharmacological interventions is the randomised controlled trial of a drug against a placebo control. Unfortunately, except in the increasingly rare situations where there are no drugs which are in general use or have any known efficacy for the disorder, there are serious ethical issues involved in subjecting participants to a placebo control because this effectively means denying them active treatment for the duration of the trial. There have been some research designs which attempt to compensate for this, for example double cross-over trials. However, even this can only be done in a limited number of disorders, for example those where a period without treatment is considered safe.

This need to provide active treatment for all research participants leads to the use of comparisons against other active drugs. These comparisons then become difficult to assess as a growing 'daisy chain' of 'Drug A against placebo, then Drug A against Drug B, then Drug B against Drug C, then Drug C against Drug D,...'

develops. It becomes impossible to know whether Drug D is indeed better than placebo, particularly if the daisy chain breaks, and one drug is discredited or any intervening research is found to be flawed. Even if this does not occur, the fact that no two research studies are ever identical means that the conclusions drawn become increasingly tenuous with respect to comparisons of one drug against others which are further along the chain.

The sad story of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents

In 2004 a meta-analysis of data out of studies of SSRIs in children and adolescents was published by Whittington and colleagues (Whittington, Kendall, Fonagy, Cottrell, Cotgrove et al. 2004). This review revealed that most of these substances have no benefit but may cause harm in minors. Alarmed by reports in the media about suicides among youths prescribed an SSRI, official regulatory authorities then conducted audits of the data from pharmaceutical companies concerning all trials and results by these trials with minors. The major results of these audits were alarming and informative. First, the pharmaceutical companies had published the results of trials very selectively: 'good news', such as data about effectiveness of SSRIs, was published, whereas 'bad news', the data about side-effects or inefficacy, was not published. Second, an analysis of all trials and published and unpublished data by Hammad and colleagues (Hammad, Laughren, & Racoosin 2006) revealed that there was an increased risk for suicidal behaviour among children and adolescents using SSRIs. This revelation has led to black-box warnings against all antidepressants and resulted in a decrease of use in some countries. The consequent decreased use is now thought to be responsible for an increase in suicides among youths and the FDA has been criticised for this outcome (Gibbons, Brown, Hur, Marcus, Bhaumik et al. 2007; Nemeroff, Kalali, Keller, Charney, Lenderts et al. 2007). This complex issue is discussed by Zito and Safer (Safer & Zito 2007) and the long-term effects of this research scandal are yet to be revealed. Publishing policy has changed since the SSRI debacle and journals have revised their policies about publishing studies showing inefficacy.

In adolescent psychiatry, this has happened for the Selective Serotonin Reuptake Inhibitor (SSRI) class of drugs for depression, where most of the drug trials pitted one SSRI against another, but almost all have been discredited because of failures to report adverse events such as suicide (see Text Box). This has left the evidence base very shaky and the withdrawal of all except one SSRI, Fluoxetine, for the treatment of depression in adolescents.

In drug trials, the gold standard is statistical design and analysis to demonstrate that the drug being tested is superior to placebo or a control active drug. With active controls, however, this may require large sample sizes. Showing equivalence is often used instead as the benchmark for trials of a new drug against an active control. Showing non-inferiority as opposed to equivalence requires a smaller sample size, and is therefore quicker and easier. Increasing the margin of definition of non-inferiority also lowers sample sizes, but increases the rate of false positives, that is, misleading results that a drug is not inferior to its control when it actually is. This creates a tension between attempting to bring down the costs and potential yield of results of research studies, against the importance that clinically valid and meaningful results are actually being obtained (“Tests for equivalence or non-inferiority – why?,” 2008).

Another way in which research design may be scientifically suboptimal is when the comparisons being made do not reflect clinical reality. This is very relevant to child and adolescent mental health, where pharmacological treatments are never used in isolation, and are usually combined with a psychological therapy. There are, however, commercial constraints which explain why naturalistic combined treatment trials are rarely funded and therefore rarely conducted. This will be discussed in the next section.

Ethical issues in commercial research interests

Pharmacological research trials are extremely expensive to set up and run. The possibility of legislation to increase the availability of approved and safe drugs for children has been discussed in the USA and Europe (Ayme and Schmidtke 2007; DiMasi and Grabowski 2007; Food & Drug Administration 2003; Grieve et al. 2005; Haefner 2007; Klein 2006; Kölch et al. 2007; Vitiello et al. 2004). An essential difference exists between the US and Europe in funding clinical trials

with minors. In Europe, given the general paucity of public research funds and the expense of interventional trials, publicly funded pharmacological research is relatively rare. In the US, legal regulations have been in existence since the 1990s to encourage the development of paediatric medications (Vitiello et al. 2004). Indeed, 11% of all medications with patent protection by the FDA granted for paediatric studies were neuropharmacological medications (Food & Drug Administration 2003). However, these regulations have also led to problems. Several studies on paediatric depression were conducted in the USA under the pressure of time before the regulation ran out. As a result, the studies are burdened with some methodical weaknesses (Klein 2006). In Europe similar legislation has been in effect since 2007, but the effects of the “EU Regulation on medicinal products for use in children” cannot yet be foreseen (Kölch et al. 2007).

Because of the paucity of public funding, pharmaceutical research remains the domain of pharmaceutical companies, which have the resources to support the development and licensing of their products and therefore fund many of the pharmacological trials that take place. These companies, however, have strong vested interests in finding their products, particularly new products still under patent, to be superior to other medications. The ultimate bottom line for pharmaceutical companies, which are commercial institutions with accountability of management to shareholders, is to create profit. Coupled with the common problem of publication bias because trials with negative results are less interesting and therefore harder to publish than positive ones, this can create significant skewing of results. Skewed results showing a spurious effect can alter clinical practice and potentially harm patients.

Researchers who are employees of pharmaceutical companies can experience moral dilemmas between maintaining scientific objectivity and the obligation to try to produce positive results that can help their employers achieve targets. Researchers who have their research or teaching activities funded by pharmaceutical companies can also experience this moral dilemma. There is a growing movement against commercially funded research and researchers, with independent experts, researchers and research being favoured as less biased (Moynihan 2003; Moynihan 2008a). In the past, pharmaceutical companies have been lavish in funding teaching, seminars and academic activities such as conference attendance for physicians. There is, however, evidence that these commercial sponsorships have an

impact on prescribing practices of physicians (Als-Nielsen et al. 2003; Angell 2004; Lexchin et al. 2003; Melander et al. 2003; Moynihan 2008b). There has a growing suspicion of commercial interests as unethical and a backlash amongst doctors against pharmaceutical sponsorship and commercially funded research. However, the real world situation is that most pharmaceutical research is funded by commercial interests. As much as commercial interests affect research, it would be even more unethical, in addition to being unfeasible, to discount or seek to dismiss all commercially funded research.

A further ethical dilemma in commercially driven research is that where there is relatively low financial gain to be had from conducting research, pharmaceutical companies are less likely to fund it. This is the case for psychopharmacological research in children and adolescents. Once a new drug is licensed for use in adults, given the lack of research evidence for drugs in adolescents and particularly children, child and adolescent psychiatrists will begin to prescribe these drugs 'off-label' to their patients. To attempt to conduct research in children and adolescents to obtain licences for these age groups would be both more complex and therefore expensive for companies, and also provide minimal additional commercial yield.

A further ethically relevant point is the need for combined treatment strategies in child and adolescent psychiatry. To improve the safety of drugs in paediatric and adolescent psychiatry, it will be essential to consider special needs of children and adolescents and to investigate the effects of combination therapies (psychopharmacotherapy and psychotherapy, or treatment with several medications). The really essential results of the last decade were found in publicly funded trials on attention-deficit/hyperactivity disorder (ADHD) and in depression (major depressive disorder, or MDD). The NIMH Multimodal Treatment Study of ADHD (also known as the MTA study) and the NIMH-funded Treatment for Adolescents with Depression Study (TADS) compared both psychotherapy and psychopharmacotherapy with the combined treatment, which is a more naturalistic approach than having two solely pharmacotherapy treatment arms (Glass 2005; Jensen et al. 2001). Funding multimodal interventional research would not be particularly interesting to pharmaceutical companies as their primary interest is in the superiority of one pharmaceutical product over another. Furthermore, in the case of comparing two substances from two different manufacturers, patent aspects may

be an important hindrance. The new European legislation has the potential to help facilitate such naturalistic trials, but to what extent such desiderata are taken into consideration by the EU regulation is being critically discussed (Baber 2005; Grieve et al. 2005). There is therefore little research funding from the companies for this particularly vulnerable patient group.

Finding a way forward

In the light of so many difficult, intertwined and disparate ethical dilemmas, it is tempting to despair of whether any psychopharmacological research in children and adolescents can ever be ethically sound. It is important that the exploration of ethical dilemmas should not end with the naming of a long list of problems and a metaphorical wringing of hands, but that some thought and energy should be given to possible ways forward.

The positive way forward in the development of ethically sound psychopharmacological research in children and adolescents is to bring research ethics into the heart of research development and design itself, rather than just using research ethics as an oversight mechanism to identify flaws and potentially block research, as is commonly the case or perception of researchers. In order for ethics to become a helpful and integral part of research, it is important that there should be a gradual change in culture and approach involving hearts and minds, rather than a change in regulations that increases the burden on researchers. Regulation is about ensuring a minimal acceptable standard; in contrast, bringing ethics into the heart of research paradigms should be about creating a maximal, gold standard of ethical and ethically-conducted research.

There are three different and complementary ways in which this can be achieved:

- A comprehensive ethical analysis which takes into account the different and conflicting ethical principles relevant to psychopharmacological research in children and adolescents;
- Conducting empirical ethics research into issues concerning psychopharmacological research in children and adolescents; and
- Building in ethical thinking and analysis into psychopharmacological research in children and adolescents.

i. A comprehensive ethical analysis

Most of the ethical principles which are relevant to psychopharmacological research in children and adolescents have been developed in other fields and for other situations, which is why there has been relatively little resolution of their conflicting implications. For example, the principle of autonomy was developed for autonomous adult patients based on an individual autonomy model based on the idea of patients making rational choices. The principle of protection of children, in contrast, has been developed from a tradition of protecting children from abuse and exploitation, in a tradition where children have been seen as having little voice or control over their situations with respect to adults who are disposed to harm rather than protect them.

A comprehensive ethical analysis would involve naming and exploring all the different principles that are relevant to this field. It would also involve having debates involving ethicists, researchers, clinicians, policymakers and patients to decide whether certain principles are imperative and immutable, and if so, which ones; or whether all the principles are relative and variable. By acknowledging the difficulties of navigating so many different and often conflicting principles, it can become possible to explicitly compare and weigh them against each other, and to be able to accommodate different situations which may require different resolutions. For example, should upholding the notion of 'minimal risk' always paramount? Or are there situations, such as in research with competent older adolescents and disorders without any known treatment where taking greater risks may potentially be balanced by having greater potential benefits, where protection may take second place to fully informed consent and great potential scientific as well as individual benefit? There needs to be open dialogue and debate about these tensions, between researchers, ethicists, research funders and policy-makers.

A final merit of a comprehensive ethical analysis is that other ethical considerations which have not been prominent in the ethical debates concerning psychopharmacological research in children and adolescents can be raised. One example of this is the issue of Altruism. The current system of ethics oversight of research, in its preoccupation with protection of research participants, does not allow for much consideration of altruism on the part of the participant. This is particularly the case when the research participants are considered vulnerable or may lack competence. When this happens, the only rationale which appears to be an acceptable justifi-

cation for research is benefit for the individual or, at most, for others who suffer from the same condition. People, however, often have more noble motives. Many children and young people are highly idealistic and altruistic, and even though their protection is important, it is also important to allow children and young people opportunities to develop a sense of citizenship and make contributions to society. It is common that those who have suffered greatly and also experienced care and support from healthcare professionals are grateful and wish to give something back to those who helped them by taking part in research. Another common altruistic sentiment that researchers often hear is that children and young people would like to contribute towards others like them having better treatment and experiencing less suffering, so that others can benefit from their experiences. This altruistic view can also have benefits for the individual in terms of his or her own narrative, as children and adolescents as well as adults taking part in research often express the wish that their own difficult and painful experiences of illness can have potential benefit for others, so that their suffering is not in vain.

ii. Empirical ethics research

Empirical ethics research is a relatively novel field, where ethicists use empirical research methods to observe the ‘real world’ dilemmas that occur around particular issues, and develop ethical analyses based on these research findings. Empirical ethics has the merit of being grounded in real life ethical dilemmas, as opposed to theoretical reasoning of what is morally right or wrong. Theoretical reasoning, while very valuable, tends to be dogmatic and may be experienced as unhelpful or out of touch by those struggling with complex ethical dilemmas as well as constraints such as limited resources. Empirical ethics research, in contrast, is more likely to capture the full complexity of their dilemmas and the concurrent constraints, and is therefore more likely to be able to generate helpful analyses and pragmatic suggestions for ethical resolution (McMillan and Hope 2008).

Examples of empirical ethics research that either has been done or would be useful to do are:

- Competence to consent to research in children and adolescents who suffer from mental disorders;
- The views of children and young people, and their parents, about research participation and what the ethical issues may be for them;

- The understanding of the nature of altruism and its place in psychopharmacological research in children and adolescents;
- The experiences of children, young people and their parents in participating in research;
- The ethical dilemmas that research staff and the patient’s clinical team experience in the course of such research.

Such empirical research can be done alongside psychopharmacological research in children and adolescents, as ‘bolt-on’ modules of research which can occur alongside the core research.

iii. Building in ethical thinking and analysis into psychopharmacological research in children and adolescents

Researchers, particularly those who labour under strict ethical oversight systems, may be driven to consider research ethics as onerous and designed to stifle research. A more healthy approach is to embrace research ethics and to consciously design ethical input into research methodology. This can be done in several ways:

- Having a research ethicist involved in developing the research design can help to ensure the development of ethical research designs and thoughtful consideration of the various ethical tensions.
- Having a steering group involving patients and parents can help researchers identify, from their perspective, what might be the relevant ethical issues, and, equally, what might be non-issues. The steering group can also help the researchers to design the study in such a way as to avoid ethical problems.
- Having a research ethicist as a consultant during the conduct of the study can ensure that any issues that arise can be considered properly and effectively dealt with.
- Having an ethicist on the data management committee which has oversight of the emerging data and may have to consider issues such as welfare of patients in the arm of a study which is showing less benefit can also be helpful.
- Conducting preliminary empirical ethics research, such as investigating patients’ and parents’ views of a controversial research design or a potentially risky but beneficial treatment, may be helpful in determining whether such research could or should be undertaken, and how this can best be achieved. Pragmatically, such preliminary research can also assist in demonstrating to ethics oversight committees that the ethical ramifications have been adequately explored.

- Bolting on empirical research studies to the main study, as described above, which has a protective effect by ensuring that the ethical dilemmas that emerge are being studied, in addition to adding to the body of knowledge about the ethics of research.

Conclusion

Research in psychopharmacology for children and adolescents is fraught with ethical problems and tensions. What is needed is both an increased awareness of the ethical issues and tensions which permeate such research, as well as a willingness to acknowledge these issues and to invest time and commitment to exploring them. Just as we need more psychopharmacological research in children and adolescents in order to develop a sound understanding of how to best treat children and adolescents with mental disorders, so we need more ethical analysis and ethics research in order to develop a sound understand of what constitutes good, ethical psychopharmacological research in children and adolescents.

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Clinical Research in Vulnerable Populations. The Legal Framework

Gerfried Fischer

I Introduction: The basic legal problem¹

There can be no doubt that the development of modern medicine would not have been possible without systematic research and that this research has included and will necessarily include human beings.² There can also be no doubt that for most diseases of children, especially younger ones, the research subjects cannot be other persons than children at about the same age.³ The same holds true for incapacitated adults, who suffer from a physical or mental condition, which exists only in this population. Doctors or other scientists, however, have no privilege to subject any person to any treatment just for the general good, but as it is said in the first sentences of the principles set out at the Nuremberg Trials: “The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent” (Fischer 1979:110) Now, most children as well as incapacitated adults needed for clinical trials do not have the

¹ Basic Literature: Fischer, *Medizinische Versuche am Menschen*, 1979; Helmchen, *Versuche mit Menschen in der Medizin, Humanwissenschaft und Politik*, 1986; Kleinsorge/Steichele/Sander, *Klinische Arzneimittelprüfung*, 1987; Schmidt-Elsaesser, *Medizinische Forschung an Kindern und Geisteskranken. Zur Strafbarkeit von Forschungseingriffen an Einwilligungsunfähigen*, 1987; Kern, *Fremdbestimmung bei der Einwilligung in ärztliche Eingriffe*, *Neue Juristische Wochenschrift (NJW)* 1994:753ff.; Freund/Heubel, *Forschung mit einwilligungsunfähigen und beschränkt einwilligungsfähigen Personen*, *Medizinrecht (MedR)* 1997:347ff.; Taupitz/Fröhlich, *Medizinische Forschung mit nichteinwilligungsfähigen Personen*, *Versicherungsrecht* 1997:911ff.; Fröhlich, *Forschung wider Willen?* 1999; Rosenau, *Legal Prerequisites for Clinical Trials under the Revised Declaration of Helsinki and the European Convention on Human Rights and Biomedicine*, *European Journal of Health Law* 7:105–121, 2000; Wachenhäuser, *Medizinische Versuche und klinische Prüfungen an Einwilligungsunfähigen*, 2001; Taupitz, *Biomedizinische Forschung zwischen Freiheit und Verantwortung. Der Entwurf eines Zusatzprotokolls über biomedizinische Forschung zum Menschenrechtsübereinkommen zur Biomedizin des Europarates*, 2002; Taupitz, *Forschung an Kindern*, *Juristenzeitung (JZ)* 2003:109ff.; Michael, *Forschung an Minderjährigen – Verfassungsrechtliche Grenzen*, 2004; Eck, *Die Zulässigkeit medizinischer Forschung an einwilligungsunfähigen Personen und ihre verfassungsrechtlichen Grenzen*, 2005; Magnus, *Medizinische Forschung an Kindern*; 2006; Deutsch/Spickhoff, *Medizinrecht*, 6. Aufl. 2008, 579ff., 745ff.

² Kennedy/Grubb, *Medical Law*, 3rd ed. 2000, 1665.

³ Comp. Schwarz/Holz-Stomczyk/Wartensleben, *Klinische Prüfungen von Arzneimitteln bei Jugendlichen, Kindern, Kleinkindern und Säuglingen*, *Pharmazeutische Industrie* 1998:386ff.; Walter-Sack/Haefeli, *Qualitätssicherung der pädiatrischen Arzneimitteltherapie durch klinische Studien*, *MedR* 2000:454ff.

legal capacity to give a responsible and valid consent themselves. So the legal problem of clinical research in vulnerable populations is whether and under what circumstances this consent can be substituted by that of a legal representative, i. e. the children's parents or the incapable adults' guardian.⁴

Here, in law as in ethics we have to distinguish between treatments which are to be tested for the patient's own good, and experiments from which the research subjects do not benefit personally and directly.⁵ On this fundamental distinction between therapeutic and non-therapeutic research not only the principles of the Declaration of Helsinki are based, but also the legal provisions for biomedical research in Germany and most other countries. The same distinction is made in the European Clinical Trials Directive and in the Convention on Human Rights and Biomedicine of the Council of Europe, also called the Bioethics Convention.

II Legal rules in German law concerning clinical trials

In German law we have two sorts of legal rules for clinical studies involving human persons. On the one side there are special statutory provisions on trials with pharmaceutical products and with medical devices, which include specific rules concerning children and incapacitated adults. On the other hand the general rules of tort and criminal law, which protect life, body and health against wrongful injuries, have to be observed. The basic special statutory rule, as laid down in § 40 AMG (Arzneimittelgesetz) and § 20 MPG (Medizinproduktegesetz), is that a drug or a medical device may only be tested on a person, which is capable of giving informed legal consent. This rule, which is directed at non-therapeutic research, is modified by § 41 AMG and § 21 MPG which govern clinical trials on persons who suffer from a disease, for the treatment of which the drug or medical device shall be applied. These are obviously the cases of therapeutical research. Here, if the patient has no full legal capacity, consent can and must be obtained

⁴ Directive 2001/20/EC of the European Parliament and of the Council of April 2001 on the approximation of the laws, regulations and administrative provisions of the Member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. O.J. 1. S. 2001, L 121/34.

⁵ Laufs, in Laufs/Uhlenbruck, *Handbuch des Arztrechts*, 3d ed. 2002, § 130 Rn. 5ff.; Deutsch/Spickhoff, *Medizinrecht*⁶, Rn. 922.

from its parents or legal guardians. In addition, the patient itself has to be asked, if it understands the nature, meaning and importance of the clinical trial.

In both statutes, i.e. AMG and MPG, we find another provision concerning children (not incapacitated adults) which allows the testing of pharmaceutical products or medical devices intended for the diagnosis of, or protection against, diseases of minors.⁶ It is somewhat misplaced in §§ 40 AMG, 20 MPG, i.e. the basic rules for non-therapeutic research. As this provision demands that the application must be indicated for the diagnosis of, or the protection from, an illness of *the* minor, there should be no doubt that it does not allow plain scientific experiments on children without personal benefit.⁷

In other fields of medical research, which do not fall under specific statutes, legal requirements and limits are set by those general rules of tort and criminal law, which protect life, body and health against wrongful injuries. Here too, parents or guardians can validly consent to trials of therapeutic, diagnostic or protective measures, as long as the child or incapacitated adult is intended to benefit from them directly. But parents and guardians are obliged to act for the best interests of the child or incapacitated person, and, as a general rule, giving their consent to non-therapeutic research is contrary to this obligation.

Looking to those rules described above we have to ask firstly where the line between therapeutic and non-therapeutic research has to be drawn and secondly whether there are exceptions to the general principle that informed consent to non-therapeutic research can only be given by the person involved, not by a legal representative.

III Therapeutic clinical research

III.1 The importance of an indication

In order to distinguish between allowed therapeutic and not allowed non-therapeutic clinical research we have to look for the indication of the measures taken.⁸ This means that phase-1-studies on healthy or sick children or incompetent adults,

⁶ § 40 (4) AMG, § 20 (4) MPG.

⁷ Habermann/Lasch/Gödicke, *Therapeutische Prüfungen an Nicht-Einwilligungsfähigen im Eilfall*, NJW 2000, 3389, 3390; Eck (n. 1), p. 84–87, 325, 342; Deutsch/Spickhoff, *Medizinrecht*⁶ no. 801, 1327. Cf. Laufs, in Laufs/Uhlenbruck, *Handbuch des Arztrechts*, 3rd. ed. 2002, § 130 Rn. 12.

⁸ Fischer (n. 1), p. 35.

which only serve to find out possibly damaging secondary effects of a drug, are not permitted.⁹ Diagnostic measures may only be tested if a concrete disease shall either be excluded or shall be treated according to the diagnostic result.

The indication, however, does not have to be an absolute one. It is sufficient that in the concrete case the success of the research treatment appears to be more probable than that of the standard treatment or, if no standard treatment exists, of a non-treatment.¹⁰ When e.g. atypical neuroleptica are tested on children, there need not be absolute certainty that they have no late secondary effects, but there must be objective reasons for such an assumption. How high then must the probability be so that the new treatment is superior to an old one or to a non-treatment? This depends on the intended benefits and on the possible damages. As long as there is no standard treatment as an alternative, small progress and low probability will suffice. Here the trial is still better than doing nothing. But the better and the safer existing treatments are the higher the benefits and the probability of their realisation have to be, especially when the omission of a standard treatment may produce irreparable damages.¹¹

III.2 Indication in controlled clinical trials

That there has to be only a relative, not an absolute indication, is of great practical importance for controlled clinical trials. Standard treatment and new treatment cannot both be absolutely indicated, but there can be a relative indication for each of them. Even among standard therapies more than one can be indicated. One may be riskier, but more effective, the other less dangerous, but also less effective. In clinical trials too there is rarely a strict either/or between standard and research treatment. The research measure may promise a higher probability of success, but on the other hand its effects cannot be predicted with the same certainty as for standard treatments. Expectations, even when based on careful planning, will not always be fulfilled. As an example I may cite a Canadian investigation on the treatment of small children against croup with cortisones. Inter alia it was tested whether inhaled cortisones were more effective than those injected. Unexpectedly the injection proved more effective, although the respiratory tracts

⁹ Deutsch/Spickhoff, *Medizinrecht*⁶, no. 959.

¹⁰ Fischer (n. 1), p. 44.

¹¹ Hart, *Heilversuch, Entwicklung therapeutischer Strategien, klinische Prüfung und Humanexperiment*, *MedR* 1994, 94ff.

are reached much faster by inhalation. For these reasons controlled clinical trials on children and incapacitated adults are possible, as long as not one of the treatments tested is ascertained to be significantly superior.¹²

III.3 Trials with placebos

The requirement of an at least relative indication sets rather important limits to the use of placebos in clinical trials involving children or incapacitated adults, for the placebo treatment of such patients will rarely be indicated.¹³ It is well known, of course, that for certain diseases there can be therapeutic effects of placebos, and where this is possible, there will be fewer damaging secondary effects from the placebo than from the verum. This possibility, however, does not open a broad way to placebo-controlled studies in vulnerable populations for the disease to be treated must be one where placebo effects show up on an increased scale. In addition to that it would have to be the purpose of the trial to establish a placebo treatment of patients suited for it if the placebo branch of the investigation should prove the more successful one. This will not very often be the case.¹⁴

Placebo treatment may, however, constitute a real advantage for those patients who shall receive the new treatment only after it has proved to be successful in the investigation. For if the results within the placebo group are better than those within the verum group or equal to them, they will spare a treatment which would otherwise wrongfully have been considered as effective. So here it depends on the design of the trial, whether children or incapacitated adults might profit from verum as well as from placebo treatment.

III.4 Measures of observation and control

As shown above, a research treatment is beneficial to a minor or incapacitated person and therefore allowed with the consent of its parents or guardian if there is at least a relative indication for it. This requirement of an indication is not limited to the treatment which is to be tested as such, but must generally be extended to all measures of

¹² Deutsch/Spickhoff, *Medizinrecht*⁶, no. 975f.; Gladke, *Klinische Prüfung bei Kindern*, in: Kleinsorge/Streichle/Sander (Hsg), *Klinische Arzneimittelpfprüfung*, 1987, p. 94f.

¹³ See also Eck (n. 1), p. 78–80; Michael (n. 1), p. 165, who would allow placebo-trials for the treatment of minor bodily complaints, obviously regardless of an indication.

¹⁴ Habermann/Lasch/Gödicke, *Therapeutische Prüfungen an Nicht-Einwilligungsfähigen im Eilfall*, NJW 2000, 3389, 3392.

observation and control. There is, of course, no objection to such measures if they are intended to avert risks, e.g. if they shall secure the early detection of damaging secondary effects. But there is no indication for and hence no benefit from measures which are used without the intention of any therapeutic consequences. This starts with trifles like extending the taking of a blood sample by some additional millilitres for a general investigation of liver reactions to a new anticonvulsivum or antiepilepticum. According to my personal opinion this is not an independent invasion of the patient's body or health and is therefore justified by the principle of "minima non curate praetor" as socially adequate at least in a university clinic.¹⁵ But this does not apply, of course, as soon as there is no indication for the taking of the blood as such or if other invasive or even only molesting measures are taken. These measures have no direct benefit to the patient. Here we cross the bridge to non-therapeutic research.

IV Non-therapeutic, i.e. not directly beneficial research

To restrict non-therapeutic clinical research to persons who are capable to consent to the measures taken, protects children and incapacitated adults from the risks, pains and damages that might result from such research. But at the same time it is a serious obstacle to the development of new treatments for these groups of patients who are unable to give a valid consent. In order to assert the efficacy of a treatment there have to be controls, from which future patients may profit, but very often not yet the test person itself. Where the controls are not allowed, future patients will be denied this profit. Consequently, for populations who because of their incompetence cannot participate in controlled clinical trials medical progress will be slower and less safe. This can result in a much higher disadvantage and sacrifice than the sacrifice brought by those patients who undergo non-therapeutic measures involving only small risks or no risks at all (if the latter is possible).

IV.1 Clinical trials on minors

a) National and international legal rules

For this reason § 41 sect. 2 of the German AMG contains a special provision for clinical trials on minors, who suffer from a sickness to which the medicinal product to be tested shall be applied. If there is no indication for the application on the

¹⁵ Fischer (n. 1), p. 25.

minor himself, it can be sufficient that the clinical trial is connected with a direct benefit for the group of patients who suffer from the same sickness as the research subject. In addition to this group benefit such research must be absolutely necessary for the confirmation of data obtained with clinical trials on other persons or by other research methods. Furthermore it must relate to a condition from which the minor concerned suffers and it must not be connected with more than minimal risks and minimal burdens. This regulation corresponds to the one which Art. 17 sect. 2 of the Bioethics Convention (European Treaty Series No. 164, 4. IV. 1997:6.) prescribes for non-therapeutic research on all persons unable to consent, minors as well as incapacitated adults. It is more restrictive than that of the European Clinical Trials Directive with regard to the risks allowed. Art. 4 lit. g of the directive only demands that “clinical trials have to be designed *to minimise* discomfort, fear and any other foreseeable risk *in relation* to the disease and development stage”. Although the expression “minimal” in the German AMG and the Bioethics Convention is open to interpretation and the opinions about what is minimal and what is more than minimal may differ, these regulations allowing only minimal risks try to set an absolute barrier, which does not depend on the importance of the trial. In contrary to this the European Clinical Trials Directive sets no more than a relative barrier. Taken literally, it means that more than minimal, even substantial damages and risks may be incurred, if only the disease is grave enough and the possible benefit for the group of patients is great enough¹⁶. This is not compatible with the legal principle that there is no general obligation to sacrifice one’s life, body or health for the benefit of other persons¹⁷. Therefore it is with good reason that the German legislation in the AMG has set a stricter risk limit than the European Clinical Trials Directive. That is an option permitted by the Directive itself, which (in Art. 3 sect.1) does not prejudice national provisions on the protection of clinical trial subjects if they are more comprehensive than the provisions of the Directive.

b) Compatibility with fundamental rights

The basic justification for the legalisation of a restricted non-therapeutic research on children results from a weighing of interests. The future interest of other chil-

¹⁶ Michael (n. 1), p.156.

¹⁷ See also Laufs, Die neue Europäische Richtlinie zur Arzneimittelprüfung und das deutsche Recht, MedR 2004, 583, 590.

dren to be cured from their diseases is given more weight than the interest of the research subjects in not being subjected to invasions of their bodily integrity or privacy, as long as those invasions involve no more than minimal burdens or risks. Whether such a weighing of interests should be admissible at all is heavily disputed, however. Persons who have legal capacity are not obliged and cannot be forced to participate in non-therapeutic research, and for this reason it is argued to be discriminating if persons without legal capacity can be subjected to such research without their own consent. Those who oppose the Bioethics Convention even maintain that in German law this would amount to an offence against human dignity protected by Art. 1 GG, because here incapable persons are used for an extraneous purpose. That is said to be degradation from a human subject to an object and therefore a violation of human dignity.¹⁸

There is a correct starting point within this argumentation. When research is done on capable persons there is no weighing and balancing of their interests in their body and health against that of other persons. Without their consent they are not obliged to the slightest sacrifice of their personal integrity, even if it would save another person's life. With this principle it is difficult to reconcile, that incompetent persons may be subjected to such a sacrifice. Without their own consent the consent of their parents or guardians is no full equivalent, as soon as these act beyond the child's or incapacitated adult's interest. So if we allow scientific experiments on these patients, we dispense with a prerequisite that we consider as indispensable for experiments with competent persons.

It has, however, been justly pointed out, that invasions on body and health must not necessarily be a violation of human dignity¹⁹. Our legal system does not completely disallow such invasions. On the contrary, Art. 2 al. 1 GG (Grundgesetz) states that interferences with life or bodily integrity must be based on a statute. It does not say that such interferences are only allowed for the subject's own benefit. The existence of the general draft to military service shows that the state can

¹⁸ Kommentar zum Entwurf der Bioethik-Konvention, Deutsche Richterzeitung (DRiZ) 1995, 150, 151; Roitzheim, Viele Fragen bleiben offen – Anmerkungen zur Biomedizin-Konvention, DRiZ 1997, 92; Deutscher Richterbund, DRiZ 1998, 374, 375; Spranger, Fremdnützige Forschung an Einwilligungsunfähigen, Bioethik und klinische Arzneimittelprüfung, MedR 2001, 238, 243f.; Wunder, Erwiderung – Unrecht durch Ungleichbehandlung oder Gleichbehandlung im Unrecht?, JZ 2001, 344, 345.

¹⁹ Picker, Menschenrettung durch Menschennutzung, JZ 2000, 693ff.; Rosenau (n. 1), EJHL 7: 114f., 2000; Taupitz, JZ 2003, 109, 116f.; Michael (n. 1), p. 125f., 158; Magnus (n. 1), p. 69; see also Bernat, Die Forschung an Einwilligungsunfähigen, RdM 2001, 99, 105; Eck (n. 1), p. 196, 198f.

impose such risks for the general good, and there are other legal regulations that point to the same conclusion. § 81 c sect. 3 StPO (Strafprozessordnung = Criminal Procedure Act) e.g. allows bodily examinations of, and taking blood samples from, children with their parents' and from incapacitated persons with their guardian's consent. It is not a prerequisite that this is done in the child's or the incapacitated person's own interest. These measures are taken for the detection of criminal actions. When balancing the protection of the general public from serious crimes on the one side against the child's interest in its bodily integrity on the other side, the former is given more weight than the latter, because the sacrifice of the child involves no more than minimal burdens and risks. If this is no violation of human dignity, why should we judge differently when the measures taken serve the treatment or protection of other children with serious diseases? From this point of view the discrimination does not result from the fact that children will be subjected to minimal risk experiments without their consent, but from the fact that there is no legal permission to subject competent persons to the same small sacrifice, if necessary. For legal considerations this change of view is of great importance. We have not longer to deal with a problem of human dignity, but with a question of equality and discrimination, which are the scope of Art. 3 GG.

In order to avoid such discrimination a statutory regulation has been proposed, which in case of highly promising research would allow minimal risk experiments with all persons suited for the treatment to be tested, regardless of their consent, provided that there are not enough volunteers.²⁰ The result would be a social duty for everyone to participate in minimal risk experiments, if they may lead to substantial medical progress. I admit that the creation of such a social duty would not violate basic human rights²¹. It would have to be created by statute in order to comply with Art. 2 GG. However, we are not forced by Art. 3 GG to create a general duty which dispenses with consent altogether. As long as experience shows that there have always been enough volunteers among competent persons suitable for biomedical research, there is no need to subject this part of the population to a social duty. On the contrary, such a duty would have some rather disadvantageous effects. For researchers there would be no great incentive to look for volunteers

²⁰ Picker, JZ 2000, 693, 705; a.A. z.B. Wunder, JZ 2001, 344ff.

²¹ Cf. Eck (n.1), p. 212 f., who argues that all measures constituting an injury to the bodily integrity and not consented to by the research subject itself violate human dignity.

and to try to win their patients' consent, if in the end they can go ahead without that consent²². What sort of proof should the ethics committee demand in order to be certain that in this respect all possible efforts have been made? Furthermore the necessity of obtaining informed consent is of great protective value. It makes sure that the requirement of minimal risks and burdens is not interpreted by the researcher too generously and that "minimal" really remains minimal.

For the same reason it is not recommendable to do away with requiring the parents' consent for minimal risk experiments with children. Even though their consent may not be in the child's own interest, the control that they are given by this requirement is exercised for the benefit of the child. They can and should decide whether they consider the risks or burdens of the experimental measures as minimal enough to allow them, or to refuse the participation if they are not convinced.

I think I have sufficiently pointed out the disadvantages of a legal solution, which would create a general social duty to participate in minimal risk experiments without consent. These disadvantages are furthermore a sufficient reason to distinguish between competent and incompetent persons. Competent persons can and do volunteer for non-therapeutic research, incompetent persons cannot. Incompetent persons are not treated differently because they are incompetent, but because such research is impossible for the benefit of this group without the creation of a social duty. Based on this reason a rule that substitutes their parents' or guardians' consent for the incompetent persons' own consent contains no discrimination. Hence the provisions contained in § 41 sect. 2 AMG and in Art. 17 sect. 2 of the Bioethics Convention do neither violate human dignity nor legal equality²³, when they allow non-therapeutic research entailing only minimal risk or burden for the research subject.

IV.2 Clinical trials on incapacitated adults

I have already pointed out that the Clinical Trials Directive is less protective to children as to the degree of risk allowed. It is more protective to incapacitated adults, because Art. 5 lit g requires that "there are grounds for expecting that administering the medicinal product to be tested will produce a bene-

²² See also Laufs, MedR 2004, 583, 590.

²³ Magnus (n. 1), p. 70.

fit to the patient outweighing the risks or will produce no risks at all". In other words in this population a benefit for the group is not sufficient to allow minimal risks. Whether non-therapeutic research is allowed, if it entails no risks at all, is doubtful. The English and the French text of Art. 5 lit g have been interpreted as allowing it²⁴, while the German version rather expresses the contrary solution²⁵. The letter is supported by consideration 4 of the Directive, which for trials on incapacitated adults demands that the direct benefit to the patient outweighs the risks. In German national law the implementation of the Directive by § 41 sect. 3 no. 1 AMG requires for these patients that the medicinal product must be indicated to save the life of the person concerned, to restore its health or to alleviate its suffering. This means that non-therapeutic research is not allowed at all²⁶.

There can be no doubt that this is a serious obstacle to the control and development of medicinal products against the special diseases of incapable adults like dementia or grave psychiatric maladies. One might ask, why clinical trials with this population are allowed only on an even more restrictive basis than with children, as consideration 4 of the Clinical Trials Directive expressly intends. Certainly medical safety and progress are equally desirable for either group. There may be one reason, however, for making this difference. This is the person who must give its consent as representative of the patient unable to consent itself. In general, parents will be closer to their children than guardians to their wards. For most parents the sacrifice of their children's life, body or health is almost a sacrifice of their own corresponding legal interests. A comparable proximity or even identity of interest is, of course, not impossible between a guardian and its adult ward, but it will be much rarer. So, as a general rule, the proxy consent of the parents is a more reliable protection of the child's interests than the consent of the guardian for his adult ward. This justifies the more restrictive solution of the Clinical Trials Directive and the German AMG with regard to incapacitated adults in comparison to minors. One might argue that the difference between the two groups is

²⁴ Taupitz, JZ 2003, 109, 111.

²⁵ Fischer, Der Einfluss der Europäischen Richtlinie 2001 zur Klinischen Prüfung von Arzneimitteln auf Versuche an Kindern und anderen einwilligungsunfähigen Personen, in: Festschrift für Hans-Ludwig Schreiber, 2003, p. 685, 689.

²⁶ Fischer, Die Prinzipien der Europäischen Richtlinie zur Prüfung von Arzneimitteln, in: Deutsch/Schreiber/Spickhoff/Taupitz, Die klinische Prüfung in der Medizin – Europäische Regelwerke auf dem Prüfstand, 2004, p. 29, 32f.; Laufs, MedR 2004, 583, 592.

not as big as just pointed out and that Art. 17 of the Bioethics Convention, which treats both groups alike, offers the better solution. But this is not the European and the German state of law right now and it cannot be changed by simply acceding to that convention. For this would lower the protection offered to incapacitated adults right now, which the Clinical Trials Directive does not allow the national EU-member states to do.

IV.3 Importance of the incapable person's own will

Before coming to the end, I want to add one more point. Even when patients cannot give a valid consent of their own to clinical trials, this does not mean, that their will is wholly irrelevant. Firstly, according to Art. 4 a), 5 a) of the European Clinical Trials Directive and to § 40 (4) no. 3, s. 2 AMG the parents' or guardians consent must represent or correspond to the minor's or incapacitated adult's presumed will, which means especially that guardians cannot consent if they know that their ward would have refused participation in the trial²⁷. Secondly, Art. 4 b, 5 b of the Clinical Trials directive requires that the legally incapable patient has received information according to its capacity of understanding. If this patient is capable of forming an opinion and of assessing this information, his explicit wish to refuse participation or to be withdrawn from the trial must be considered by the investigator. In the stricter text of § 40 (4) no. 3 s. 3 AMG this means that the refusal has to be respected. Especially for trials without direct personal benefit heteronomy is only tolerable insofar as the research subject's consent must be substituted by that of a representative, because the intellectual or emotional capacity is not sufficient to understand the importance of the trial. As far as the patient's understanding goes, its autonomy must prevail.

V Summary

For clinical research on children and on incapacitated adults there are stricter limits than for research on other subjects. All clinical trials with these populations may only be undertaken, if they relate to their clinical condition and if they cannot be undertaken on adults able to give informed consent.

²⁷ For the importance of the incapable subject's will under constitutional law see also Michael (n. 1), p. 153ff.

Therapeutic clinical trials, which mean trials with direct benefit for the research subject, are admitted by German and European law on minors and incapacitated adults with the consent of their legal representatives. They include all measures which are indicated to improve or restore the individual research person's health. A relative indication is sufficient, so that of different treatments either one may be indicated. Measures with no direct benefit to the research subject to be expected are non-therapeutic.

Non-therapeutic clinical trials on minors according to German law are admitted with their parents' consent if some direct benefit for the group of patients is obtained and the research entails only minimal risk and minimal burden for the individual concerned. Non-therapeutic research on incapacitated adults is not admitted at all, if it entails any interference with the individual subject's bodily integrity, health or well-being, even if there is no risk.

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Regulation (EC) No 1901/2006 on Medicinal Products for Paediatric Use & Clinical Research in Vulnerable Populations

Birka Lehmann

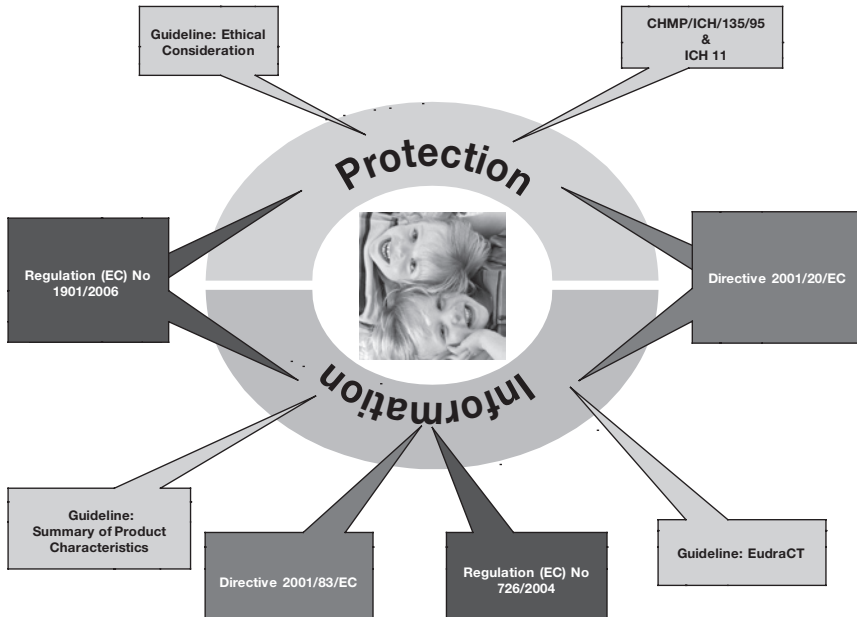


Figure 1: Authorisation of medicinal products for children, conduction of clinical trials in the paediatric population, transparency measures and information.

Introduction

The introduction reflects the statements and justification given by the European Commission for the development of the Regulation (EC) No. 1901/2006.

Since the early 1990s of the last century some aspects in the handling of medicinal products by regulators, industry and health professionals were scrutinized by patients, care givers and paediatricians in respect to the treatment of chil-

dren in all age groups. In the 27 Member States of the European Union (EU), the paediatric population represents over 20% of the total population laying down the definition of paediatric population to the age range from 0 to the end of the age of 17.

In contrast to the situation of adults, more than 50% of the medicinal products used to treat children in Europe have not been tested and are not authorised for the use in children. Therefore the health and thereof the quality of life of the children may suffer from a lack useful age appropriate medicinal products.

The paediatric population is not a homogeneous group; it ranges from pre-term newborns, through toddlers and children to adolescents. These are not miniature versions of adults. Due to age-related differences in drug handling or drug effects which may lead to different dose requirements to achieve efficacy or to avoid adverse reactions, specific clinical trials in paediatric populations are normally required. In addition, there may be practical problems of administration, e.g. difficulties swallowing tablets if a syrup is not available or, more significantly, serious calculation errors when using adult formulations to obtain paediatric dosages. Children are a vulnerable group with developmental, physiological and psychological differences from adults, which makes age and development related research of medicinal products particularly important.

Although there may be concerns voiced about conducting trials in the paediatric population, this has to be balanced by the ethical issues related to giving medicinal products to a population in which they have not been tested and therefore their effects, positive or negative, are unknown. In order to address the concerns about trials in children it has to be pointed out that the requirements for the protection of the paediatric population who take part in clinical trials in the Community laid down in the Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001. The regulation lays down rules concerning the development of medicinal products for human use in order to meet the specific therapeutic needs of the paediatric population, without subjecting the paediatric population to unnecessary clinical or other trials and in compliance with the Directive 2001/20/EC.

In terms of both public health and ethics, it is clearly preferable to test medicinal products in children, in a safe and controlled clinical trial environment where the individual child is protected and the studies generate data and information for the

benefit of the rest of the children of the EU than to go on with the daily “experiments on children” that occur today because such medicinal products for children have never been designed and evaluated for this particular use.¹

In order to increase the availability of information on the use of medicinal products in the paediatric population and to avoid unnecessary repetition of studies, the European database in Article 11 of Directive 2001/20/EC should include a European register of clinical trials of medicinal products for paediatric use – part of the information – should be made public by the Agency.

Industry has a free choice as to what kind of medicinal products to develop, authorise and market. The main drivers of an overall return on investment are the size of the target pharmaceutical market and the price achievable within this market-place. The number of children suffering of specific diseases is generally lower than the number of adults and, in terms of research, “children” can not be considered as a single population (consider a premature new-borne compared to a fifteen-year old) and therefore studies may be more complex. The current situation in the EU regarding medicinal products for children obviously shows that market forces alone have proved insufficient to stimulate adequate research into and authorisation of medicinal products for children. Thus, the industry has considered that for many childhood diseases the potential return is insufficient to justify such investment in research and development.

The overall policy objective is to improve the health of the children of Europe by increasing the research, development and authorisation of medicinal products for use in children. General objectives are to:

- increase the development of medicinal products for use in children,
- ensure that medicinal products used to treat children are subject to high quality research,
- ensure that medicinal products used to treat children are appropriately authorised for use in children,
- improve the information available on the use of medicinal products in children.
- achieve these objectives without subjecting children to unnecessary clinical trials and in full compliance with the EU Clinical Trials Directive.

¹ http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/medchild_key_en.htm (26/9/2008).

To ensure that all the medicinal products required by children fall within the scope of the proposal and to fully understand the measures proposed, it is necessary to break medicinal products down into three groups:

- products in development (not yet to be authorised);
- authorised products still covered by patents or supplementary protection certificates;
- authorised products no longer covered by these instruments.

The proposal contains a package of measures to achieve its objectives both in terms of procedural aspects and regulatory and technical requirements. The regulation comprises several core elements in respect to the collection of information on medicinal products, supported by a variety of rewards, incentives and penalties, the Paediatric Committee and transparency measures.

1 CORE element: Data collection and verification

The regulation reflects on three different actual situations for the collection of data for medicinal products in relation to the use in children. The aspect of the collection of data in the off-label use as required by Article 42 of the regulation has to be handled separately. For the moment no comments how to fulfil these measurements are released from the Paediatric Committee as requested by the regulation.

Firstly, the retrospective collection of information in accordance with Article 45 where it obliges the marketing authorisation holder of a medicinal product to provide all information regarding clinical trials in children which are already completed at latest by 26th January 2008 to the competent authorities. The submitted data and the references to these data in the corresponding package leaflet and Summary of Product Characteristics will be evaluated in the framework of Paediatric Work-sharing Programme hosted by the coordination group (CMD)². Secondly, all on-going clinical trials have to be submitted within six months of their completion according to Article 46. The third and far-reaching measures are laid down in Articles 7 and 8 of the regulation. Article 7 requires that by 26th July 2008 all applications of new medicinal products will only be validated by the com-

² <http://www.hma.eu/213.html> (26/9/2008).

petent authorities with a Paediatric Investigation Plan (PIP) and results of studies according to this PIP or a PIP deferral of a PIP waiver.

The same applies for extensions of an already authorised medicinal product with a Supplementary Protection Certificate or a Patent according to Article 8 from 26th January 2009 onwards. An additional tool to improve the knowledge about medicinal products in the use of children is laid down in Article 30, the so-called Paediatric Use Marketing Authorisation (PUMA) where data exclusivity for off patent medicinal products are offered for authorised medicinal as an incentive.

All information which will be collected in the different routes of getting relevant recommendation to treat children with a medicinal product will be included in the Package Leaflet and Summary of Product Characteristics for each corresponding medicinal product in question.

2 CORE element: Rewards, incentives, penalties, and sanctions

2.1 Rewards and incentives (Articles 36–40)

The regulation contains a shared responsibility between the European Commission and its Member States in respect of incentives for research and development of medicinal products for paediatric use and for placing such products on the market, within the framework of their own powers and responsibilities.

The requirement for data in children applies to the current procedures for marketing authorisation applications; the reward for compliance with the requirement is an extension to the existing supplementary protection certificate (SPC); for orphan medicinal products the reward for compliance with the requirement is two years added to the existing market exclusivity; the new type of marketing authorisation, the PUMA, utilises the current marketing authorisation procedures.

2.1.1 EU – Patent protection, certificate of suitability, market exclusivity, data exclusivity

For new medicinal products or line extensions of existing patented medicinal products, covered by a patent or a SPC, if all the measures included in the agreed paediatric investigation plan are complied with and if the product is authorised in all Member States and if relevant information on the results of studies is included in product information, the six-month SPC extension will be granted.

As the reward is for conducting studies in children and not for demonstrating that a product is safe and effective in children, the reward will be granted even when a paediatric indication is not granted. For orphan medicinal products a two-year extra market exclusivity will be rewarded. Under the EU orphan regulation, medicinal products designated as orphan medicinal products gain ten years of market exclusivity on the granting of a marketing authorisation in the orphan indication. Therefore it is proposed to extend the ten-year period of orphan market exclusivity to twelve years if the requirements for data on use in children are fully met.

The Paediatric Use Marketing Authorisation will utilise existing marketing authorisation procedures but is specifically developed for medicinal products exclusively for use in children. By allowing retention of the existing brand name and a benefit for the data protection, time of ten years associated with a new marketing authorisation will be rewarded.

2.1.2 Member States

The rewards and incentives included in the regulation do not preclude access of medicinal products being developed for children other incentives or rewards by Member States. It is within their respective spheres of competence, to provide other incentives for developing medicinal products for paediatric use. Member States are asked to provide information in this respect to the European Commission by a given time point and are asked to update the European Commission on a regularly basis.

2.2 Penalties and sanctions (Article 49–50)

2.2.1 EU

At the Agency's request, the Commission may impose financial penalties for infringement of the provisions of this Regulation or the implementing measures adopted pursuant to it in relation to medicinal products authorised through the procedure laid down in Regulation (EC) No 726/2004. The maximum amounts as well as the conditions and methods for collection of these penalties shall be laid down in accordance with the procedure referred to in Article 51(2) of this Regulation.

The Commission shall make public the names of anyone infringing the provisions of this Regulation or of any implementing measures adopted pursuant to it and the amounts of and reasons for the financial penalties imposed.

2.2.2 Member States

Without prejudice to the Protocol on the Privileges and Immunities of the European Communities, each Member State shall determine the penalties to be applied for infringement of the provisions of this Regulation or the implementing measures adopted pursuant to it in relation to medicinal products authorised through the procedures laid down in Directive 2001/83/EC and shall take all measures necessary for their implementation. The penalties shall be effective, proportionate and dissuasive.

Member States should have informed the Commission of these provisions by 26th October 2007. They shall notify any subsequent alterations as soon as possible and the Member States are obliged to inform the Commission immediately of any litigation instituted for infringement of this Regulation.

3 CORE element: Implementation of the Paediatric Committee (PDCO) – Composition and tasks of the PDCO (Article 5–6)

3. 1. Composition

Regarding the composition of the new Paediatric Committee two aspects have to be taken into account by ensuring the continuity in the scientific and ethical considerations of the medicinal product in question.

The continuity of the scientific aspects is assured by the requirement that five members of the PDCO are also members of the Committee for Human Medicinal Product (CHMP), the opinion taking body in a marketing authorisation procedure for medicinal products. For the moment, only the four members from Romania, Estonia, Lithuania, Slovak Republic are building the link. For the second aspect patients/parents and health professionals representatives are participating in the PDCO. Additionally, each member has an alternate.

3.2 Tasks

The PDCO is asked to

- assess and formulate opinions on Paediatric Investigation Plans, waivers and deferrals including consideration of whether proposed studies can be expected

to be of significant therapeutic benefit and/or fulfil a therapeutic need of the paediatric population,

- advice on surveys regarding existing paediatric use,
- support of the EMEA regarding the network of paediatric experts,
- providing advice (on request),
- establishment of an inventory of paediatric needs,
- recommendation on a symbol.

3.3 Paediatric Investigation Plan (PIP)

The new key element of the regulation is the early involvement of a company independent scientific and regulatory body, the PDCO, in the research and development programme of a medicinal product by the requirement to receive an agreement/a decision on the proposed process for a new medicinal product which contains two elements either to get a waiver or an agreement on the clinical trials, and if necessary including a deferral, in children to be included in the development programme.

The aim is to ensure that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population. The timing and the measures proposed to assess quality, safety and efficacy in all subsets of the paediatric population that may be concerned shall be presented in a PIP dossier. In addition, any measures to adapt the formulation of the medicinal product for its use in the paediatric population shall be included.

3.4 Other Tasks as mentioned in 3.2

3.4.1 Survey regarding Paediatric Use and Inventory of Paediatric Needs

The complexity regarding the collection of already existing information on clinical trials for medicinal products are described in section 1. Core element: Data collection and verification³. An additional task is the definition and completion of the paediatric need list. The EMEA has already published a list of medicinal products and indications where additional information for the paediatric population is needed.⁴ This information will be the underlying information for the devel-

³ <http://www.emea.europa.eu/htms/human/paediatrics/prioritylist.htm> (26/9/2008).

⁴ <http://www.emea.europa.eu/htms/human/paediatrics/inventory.htm> (26/9/2008).

opment programme of the Research Directorate-General of the European Commission for the funding of clinical trials in the paediatric population where further data are needed.

3.4.2 Scientific advice

The regulation addresses the need for supporting companies in the devolvement of medicinal products for the paediatric population by the recommendation that scientific advice should be given by the PDCO free off charge.⁵

3.4.3 Network of paediatric experts

Clinical trials in the paediatric population may require specific expertise, specific methodology and, in some cases, specific facilities and should be carried out by appropriately trained investigators. It is proposed to create a Community network to link together existing national networks and clinical trial centres in order to build up the necessary competences at a European level and to facilitate the conduct of studies, including clinical trials, to increase cooperation and avoid duplication of studies. The European Medicines Products Agency (EMA) and the Paediatric Committee will be charged with adopting an implementing strategy to establish this network. This will contribute to the work of strengthening the foundations of the European Research Area (ERA), should benefit the paediatric clinical trial population and act as a resource for industry.⁶

3.4.4 Recommendation on a symbol

The European Commission published on 30th January 2008 the following statement: Article 32 of the Paediatric Regulation (Regulation (EC) No 1901/2006) foresees that medicinal products granted a marketing authorisation for a paediatric indication shall display a symbol for their identification. Following this Regulation, the selection of the symbol by the European Commission is to be based on a recommendation of the European Medicines Products Agency Paediatric Committee. The Regulation provides for the Commission to select the symbol by 26th January 2008 and make the symbol public. On the 20th of December 2007 the Pae-

⁵ http://www.emea.europa.eu/htms/human/paediatrics/sci_advice.htm (26/9/2008).

⁶ <http://www.emea.europa.eu/htms/human/paediatrics/network.htm> (26/9/2008).

diatric Committee adopted its recommendation regarding the symbol by a majority vote of eighteen against four. The adopted recommendation is that

[A]s a consequence of its analysis balance of benefits and risks of the symbol, the Paediatric Committee was unable to recommend to the European Commission any symbol for which the benefits would outweigh the risks identified and dominated by potentially fatal medication errors'. Publication of this announcement serves to inform stakeholders that on the basis of this recommendation, the European Commission is at present not in a position to select a symbol and the provisions of Article 32 of the Paediatric Regulation can therefore not be implemented.⁷

Thus, it is unclear for the moment in which way this provision shall be handled by the Member States as this also applies to medicinal products authorised before this Regulation came into force, and to medicinal products authorised after the entry of this Regulation but before the symbol has been made public, if they are authorised for paediatric indications. In this case, the symbol and the explanation shall be included in the labelling and, respectively, the package leaflet of the medicinal products concerned not later than two years after the symbol has been made public (Article 31(2)).

4 Transparency and information (Article 41 and 28)

One of the objectives of the regulation is to increase the information available on the use of medicinal products for children. With this measure the safe and effective use of medicinal products for children can be increased and, thus, promote public health. In addition, availability of this information will help prevent the duplication of studies in children and the conduct of unnecessary studies. One of the measures is to build on the public health work of the Clinical Trials Directive. The Clinical Trials Directive establishes a Community database of clinical trials (EudraCT).

4.1 Transparency regarding clinical trials

Article 41 of the regulation requires the Commission to draw up guidance on the nature of the information on paediatric clinical trials to be entered into the database of clinical trials (EudraCT), created by Directive 2001/20/EC, on which information shall be made available to the public, on how clinical trials results

⁷ http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/medchild_key_en.htm (26/9/2008).

shall be submitted and be made public and on the EMEA's responsibilities and tasks in this regard.

The aim of the new regulation is also to increase transparency in respect to clinical trials in children in all phases of the progress, beginning from the planning and recruiting of patients to the on-going and finalised studies. The ethical requirement goes much beyond the requests presented in the Directive 2001/02/EC where the access to the European database on clinical trials is limited to the competent authorities of the Member States, the European Medicines Products Agency and the European Commission and in Regulation (EC) No. 726/2004 Article 57 which is only reflecting on the publication of information on clinical trials for already authorised medicinal products.

The European Commission published a consultation on a "Draft Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the EMEA, in accordance with article 41 of Regulation No. (EC) 1901/2006".

4.2 Information

Article 28 of the regulation sets out where authorisation is granted, the results of all those studies shall be included in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product, provided that the competent authority deems the information to be of use to patients, whether or not all the paediatric indications concerned were approved by the competent authority. Where a marketing authorisation is granted or varied, any waiver or deferral which has been granted pursuant to this Regulation shall be recorded in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned. If the application complies with all the measures contained in the agreed completed paediatric investigation plan and if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed paediatric investigation plan, the competent authority shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan. For the purpose of the application of Article 45(3), this statement shall also indicate whether significant studies contained in the agreed Paediatric Investigation Plan have been completed after the entry into force of this Regulation.

This has to be transposed by the revision of the guideline on the Summary of Product Characteristics. In this respect the European Commission realised a public consultation in the beginning of 2008. The finalisation of the revision is still pending.

5 Supporting measures – Guidelines

5.1. Guideline on ethical consideration

To contribute to the protection of children who are the subject of clinical trials a specific recommendation was deemed to be necessary. Furthermore, the recommendations are intended to facilitate a harmonised application of rules on clinical trials across the EU and thereby facilitate the conduct of clinical trials in the EU. Therefore, the European Commission realised a guideline on ‘Ethical considerations for clinical trials on medicinal products conducted with the paediatric population’– Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.⁸

5.2 Guidelines on clinical trials

Additionally, all guidelines containing recommendations on clinical trials for specific indication have to be carefully scrutinized and updated in respect to the requirements for conducting clinical trials in the paediatric population taking into account the different age groups.⁹

Conclusion

The new Regulation on medicinal products for paediatric use has to be seen in the legal framework for clinical trials and marketing authorisation for medicinal products and the supporting measure like guidance and guidelines. The paediatric population is a vulnerable group with developmental, physiological and psychological differences in itself and from adults, which makes age and development related research of medicinal products particularly important. Therefore, the con-

⁸ http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/medchild_key_en.htm (26/9/2008).

⁹ http://www.emea.europa.eu/htms/human/paediatrics/sci_gui.htm (26/9/2008).

cerns voiced about conducting trials in the paediatric population has to be balanced by the ethical issues related to giving medicinal products to the paediatric population in which they have not been tested and therefore their effects, positive or negative, are unknown.

The requirements for the protection of the paediatric population who take part in clinical trials in the Community are laid down in Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001. The regulation lays down rules concerning the development of medicinal products for human use in order to meet the specific therapeutic needs of the paediatric population, without subjecting the paediatric population to unnecessary clinical or other trials and in compliance with Directive 2001/20/EC.

Additionally, harmonised ethical considerations are published by the European Commission to be taken into account by all interested parties conducting clinical trials in children and adolescents.

It is now of utmost importance to set the scene in the European Union to convince the paediatric patients, parents, caretaker, nurses and doctors to consent in participating in clinical trials for the benefit of the paediatric population by large.

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Recent Developments and Strategies in Pediatric Pharmacology Research¹

Benedetto Vitiello

Abstract

Research in pediatric pharmacology has undergone major changes in the last ten years, with an expansion in both publicly and privately funded activities. A number of pharmacokinetics studies and multi-site controlled efficacy trials have been conducted, so that treatment of children and adolescents can now be better informed and evidence-based. Regulatory financial incentives to industry in return for studies on drugs still covered by patent exclusivity have resulted in a substantial increase in pediatric research funded by pharmaceutical companies. In parallel, public funding has supported research on off-patent medications and other clinically important aspects of treatment, such as comparisons between active treatments, including non-pharmacological interventions. With greater interest by industry in pediatric research, the role of government funding agencies has been redefined to avoid duplication and ensure better integration of efforts and utilization of resources. The present review discusses some of the recent developments in pediatric pharmacology with focus on psychiatric medications.

The last ten years have witnessed both a significant expansion of pediatric pharmacology research and a redefinition of the roles of public and private sources in supporting such research. Traditionally a neglected area of medicine, research on medication effects in children has been brought to the center of the attention in the 1990s, when the realization that the pediatric use of medications was expanding without adequate evidence for efficacy and safety spurred a number of initiatives in the U.S. (American Academy of Pediatrics Committee on Drugs 1996; Vitiello & Jensen 1997; Jensen et al. 1999; Vitiello 2007).

¹ The opinions and assertions contained in this report are the private views of the author and are not to be construed as official or as reflecting the views of the National Institute of Mental Health, the National Institutes of Health, or the Department of Health and Human Services.

On one hand, the National Institutes of Health (NIH) established research networks devoted to testing in children the pharmacokinetics, efficacy, and safety of commonly prescribed medications that were approved by the U.S. Food and Drug Administration (FDA) only for adult use (“off-label use”) (Cohen 1999; Vitiello 2006). On the other hand, legislation was enacted to provide incentives to the pharmaceutical industry for sponsoring pediatric studies (U.S. Congress 1997, 2002, 2003, 2007). As a consequence, a variety of funding sources and possible strategies has become available for conducting systematic investigations in child and adolescent pharmacology. The aim of this review is to discuss some of the recent developments in pediatric pharmacology research, and examine strategies and approaches to conducting investigations in children with special focus on psychopharmacology.

Publicly funded research

Most of the funding in pediatric pharmacology research by the NIH is provided through investigator-initiated grant applications, which undergo rigorous peer-review. Over the years, this mechanism has supported a large part of pharmacology research relevant to children. In fact, prior to the legislative changes of 1997 (U.S. Congress 1997), industry had little interest in pediatric research, even in the case of widely used medications. For example, the first trial showing the efficacy of fluoxetine in childhood depression was funded through a public grant (Emslie et al. 1997).

Besides funding investigator-initiated research, NIH launched a number of initiatives in areas of high public health significance. In the mid-1990s, research networks were started to specifically investigate pediatric pharmacology. The Pediatric Pharmacology Research Units (PPRUs) and the Research Units on Pediatric Psychopharmacology (RUPPs) were funded by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), respectively (Vitiello 2007; Cohen 1999). The PPRUs have focused on evaluating the pharmacokinetics and efficacy of drugs commonly used in general pediatrics, and thus provided an infrastructure of highly specialized academic research settings where both NIH- and industry-funded studies can be conducted (Blumer et al. 2005; Blumer et al. 2008).

Also based at academic sites, the RUPPs conducted controlled clinical trials of the efficacy of psychiatric medications used off-label in the community, such as

the selective serotonin reuptake inhibitor (SSRI) fluvoxamine for the treatment of pediatric anxiety disorders and the antipsychotic risperidone in children with autism and severe behavioral problems (Research Units on Pediatric Psychopharmacology Autism Network 2002; Research Units on Pediatric Psychopharmacology Anxiety Study Group 2001). In addition to research networks, NIMH has funded multisite clinical trials to address specific questions of high clinical relevance to the treatment of children with attention deficit/hyperactivity disorder (ADHD), adolescent depression, early onset schizophrenia, anxiety disorders, and bipolar disorder (Cohen 1999; Greenhill 2006; McClellan 2007; The MTA Cooperative Group 1999; Treatment for Adolescents with Depression Study 1999; Brent et al. 2008).

The increasing interest of industry in conducting pediatric studies that had been traditionally supported by NIH had led to a redefinition of the role of public funding, which is now focused on investigating important aspects of pharmacology that go beyond traditional pharmacokinetics or efficacy testing versus placebo. In particular, comparisons of the effectiveness of alternative specific interventions and treatment strategies have been the object of recent NIMH clinical trials with the aim of providing clinicians and families with the data necessary for informed treatment decisions. Thus, in the case of ADHD and adolescent depression, conditions for which both pharmacological and psychotherapeutic interventions are available, NIMH funded large trials to compare the effectiveness of these treatments used as monotherapy or in combination (The MTA Cooperative Group 1999; Treatment for Adolescents with Depression Study 2004). These studies have also produced informative cost-effectiveness analyses (Jensen et al. 2005; Domino et al. 2003).

Other areas relevant to pediatric pharmacology that currently receive limited attention from industry include: a) the development of treatments for autism, other pervasive developmental disorders, and rare disorders such as Tourette's disorder and child schizophrenia; b) pharmacoepidemiology research; c) meta-analyses; d) bioethics research; e) development of novel methodological tools to assess treatment effects and safety; and f) evaluations of the impact of treatment on long-term illness trajectories and distal prognosis (Vitiello 2007; Vitiello et al. 2004). Finally, as discussed more in details further down, a specific role of NIH under the Best Pharmaceuticals for Children Act of 2002 (U.S. Congress 2002) is to sup-

port pediatric studies of off-patent drugs, thus integrating and complementing the exclusivity extension initiative that applies to patented drugs.

Industry-funded research

As mentioned, the involvement of industry in pediatric research had been rather limited until the late 1990s. This situation substantially changed in the U.S. with the enactment of legislation providing pharmaceutical companies with an additional six months of drug patent exclusivity protection in return for conducting specific studies in children (U.S. Congress 1997). The legislation, initially enacted in 1997, and then confirmed and expanded in 2002 and 2007 (U.S. Congress 2002; U.S. Congress 2007), has provided a powerful incentive for industry-funded pediatric research. For example, while NIMH had been the almost exclusive source of funding for pediatric studies of psychotropic medications, industry has been funding most of the placebo-controlled efficacy trials of stimulants and anti-depressants during the last ten years, thus providing the data for recent meta-analyses conducted by the FDA and academic researchers (Mosholder & Willy 2006; Hammad et al. 2006; Bridge et al. 2007).

The exclusivity extension program has been successful in stimulating industry-funded research in pediatric pharmacology in the U.S. and similar legislation has been recently introduced in Europe (Roberts et al. 2003; Kolch et al. 2007). Knowledge of the medication dosing appropriate to children has been expanded (Rodriguez et al. 2008). From 1998 through May 2008, more than three hundred studies have been conducted and 148 changes in drug labeling implemented consequent to research conducted by industry under the pediatric exclusivity program (U.S. Food and Drug Administration 2008). About half of these studies were aimed at testing efficacy, a third at examining pharmacokinetics, and one fifth at evaluating safety.

An independent analysis of the economic cost and return to industry of the pediatric exclusivity program indicates that both cost and return are variable (Li et al. 2007). When research conducted on nine drugs was considered, the cost to industry ranged from \$5 to \$44 million, with a median of \$12.3 million. The net return ranged from \$9 to \$508 million, with a median of \$140 million, and the ratio return/cost went from -0.68 to 73.63. Obviously, the return depends on the magnitude of the overall market of the drug, including both pediatric and adult

market. Thus, in the case of a widely prescribed antidepressant, pediatric studies with a cost of \$50 million translated into a return of \$242 million, for return/cost ratio of 7 (Li et al. 2007).

Notwithstanding the overall success of the pediatric exclusivity program in fostering research, a number of limitations have been identified and several concerns raised, some of which have been addressed during the re-authorization of the program. Because the exclusivity is granted for completing specific studies within a certain period of time, but not necessarily for demonstrating efficacy, there may be pressure to conduct studies quickly, and ensuring high quality of research under time pressure can be challenging. Moreover, it was observed that the types of studies conducted under the pediatric exclusivity program tend to match more adult use than actual pediatric needs (Boots et al. 2007).

Concern was also raised that, as typical for industry-sponsored research, the data belong to the sponsor, and results may not be necessarily or promptly published, or the publications may be influenced by the source of funding (Benjamin et al. 2006; Als-Nielsen 2003; Tongeji & Poole 2007; Turner et al. 2008). Newly enacted legislation tries to address this concern by mandating that the results of all the pediatric studies conducted under the exclusivity program be posted on the FDA Website. More in general, the reported association between sponsorship and research outcome should provide further impetus to supporting publicly funded research programs as a way to both counterbalance and complement industry-funded research.

In addition to research conducted under the pediatric exclusivity program, there has been an increased interest of pharmaceutical companies in developing and testing medications for children. In fact, the increased pediatric use of medications has created, in some cases, a sizeable enough market to justify funding research programs specifically focused on pediatrics. For instance, the use of medications for ADHD has considerably increased over the years, thus making ADHD the object of novel treatment development, as shown by the introduction into the market of atomoxetine and of several new preparations of stimulants (Michelson et al. 2002). Likewise, the realization that autism spectrum disorders are much more common than once thought is stimulating industry to conduct research of potential treatments for these conditions.

The Pediatric Research Equity Act of 2003 (U.S. Congress 2003) gives FDA the authority to request that pharmaceutical companies pursuing a new drug registration for adult indications conduct also pediatric studies whenever the medication is potentially relevant to pediatric use. This act is expected to address the need for information in pediatric pharmacology prospectively and proactively, before drugs actually enter the market, thus preventing or minimizing off-label use. The full impact of this initiative will take a few years to be evaluated.

A Multiple Party Process

Successful implementation of pediatric pharmacology research depends on a close interplay among multiple parties, and most notably NIH, FDA, industry, and academic investigators (Michelson et al. 2002). For drugs that are currently marketed and still covered by patent, pediatric studies can be conducted by industry under agreement with the FDA in return for a six-month extension of patent exclusivity. For drugs currently marketed but already off-patent, the NIH and FDA collaborate towards reviewing the need for pediatric research and preparing an annual priority list, based on which FDA requests specific studies of industry (Taylor-Zapata 2007). However, because these drugs are off patent, there are few financial incentives to conduct research, and these requests are often rejected. In these cases, NIH takes responsibility for organizing and funding the studies. This process was recently followed for funding a series of studies that are now in progress to evaluate the pharmacokinetics and efficacy of lithium in the treatment of children with bipolar disorder. Finally, for drugs that are still in a pre-registration phase of development and not yet marketed, FDA can request pediatric studies as appropriate. Thus, the recently introduced regulations provide a truly comprehensive process that covers medications in different stages of development and marketing.

While integration and coordination of efforts and activities between government agencies and industry is critical, there are other parties whose role is essential for pediatric pharmacology research. Designing and conducting pediatric research require specific knowledge of methodology and bioethics, and therefore rely on the availability of a properly trained cadre of investigators who have acquired the necessary expertise. Even though the number of pediatric investigators has increased over recent years, pediatric pharmacology remains a relatively small field with limited capacity.

Another critical component is the participation of children and their families in pediatric research. Children are considered a vulnerable population for research purposes and special regulations must be followed for conducting pediatric research (Vitiello 2003). The recent expansion of pediatric pharmacology research has brought attention to the need for better understanding the critical elements of child research participation and improving the implementation and validity of the relevant bioethical procedures (Vitiello 2008). Enrollment in clinical trials is often a slow process that takes several years to be completed. Various strategies for engaging both practitioners and potential research participants have been proposed, and greater attention on the part of researchers to the perspectives and needs of children and families have been recommended (March et al. 2005; Hinshaw et al. 2004).

Conclusions

Knowledge on the effects of medications in children has significantly expanded in recent years due to an increase in publicly funded research and legislative initiatives providing financial incentives to industry. Further progress will depend on coordination and integration of efforts across the different parties. Both a public and private vigorous involvement in pediatric research is needed to address the diverse and complex medical needs of children.

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Pharmaceutical research in paediatric populations and the new EU Paediatric Legislation. An industry perspective¹

Philippe Auby

Abstract

A large proportion of medicines used in children are prescribed off-label, and children have often been denied access to new or innovative medications. Because such a situation is unethical, the need to obtain paediatric information for medicines used in children seems nowadays a matter of consensus on a global basis. Based on this, it was clear in the EU, like what has happened in the US, that there was a need for a legal obligation for pharmaceutical companies to perform studies. This new European Paediatric Regulation that entered into force in 2007 opens a new era of European drug regulatory history and will offer a major opportunity to improve children's health through advancements in research by providing a new framework for evaluating the efficacy and safety of medicines for children. But, paediatric development remains challenging and the hurdles of conducting research in paediatric population are numerous.

Background

A large proportion of medicines used in children are prescribed outside the terms of the drug license i.e. off-label, which can place children at a direct risk of under- or overdosing and a delayed risk of long-term adverse effects. Many generations of paediatricians and other physicians have learned to live with this situation (Hoppp 2008).

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This off-label use of medicines in children has, however, been an increasing concern over the last decade leading to recognize that such situation was unethical as children have not access to medications properly assessed. In 1994, the United States implemented the “Pediatric Rule” which paved the way for legislation aimed at producing drugs for children.

In 2000 in the European Union (EU), fifty per cent or more of medicines used in children have never been studied in this population but only in adults, and not necessarily in the same indication (or the same disease) (Conroy et al. 2000). Even if paediatric clinical studies have been performed in some cases, very few medicinal products used have a paediatric indication and a defined posology, and even less a formulation allowing the administration to young children.

The need for more studies to obtain paediatric information for medicines used in children seems a matter of consensus on a global basis nowadays (EMA 2007). Based on this, it was clear in the EU that there was a need for a legal obligation for pharmaceutical companies to perform studies if they intended to develop medicines for use in the paediatric population (EMA 2007).

The New European Paediatric Legislation

A new legislation governing the development and authorisation of medicines for paediatric use (children and adolescents aged 0 to 17 years) was introduced in the EU in December 2006 and entered into force in January 2007 (European Commission 2006). The goals of the EU legislation are the same as in the US paediatric legislation, i.e. to improve children’s health through advancements in research and to provide a new framework for evaluating the efficacy and safety of medicines for children. However, unlike in the US, the EU legislation is leading to faster and more profound changes in the field of paediatric development in Europe. The timelines of obligation for pharmaceutical companies are:

- 18 months from entry into force (July 2008), applications for new marketing authorisation applications (new products) should contain results of studies conducted in compliance with agreed Paediatric Investigation Plan (PIP) unless waiver or deferral;
- 24 months from entry into force (January 2009), application for new indications, new routes of administration or new pharmaceutical forms should contain results of studies in compliance with agreed PIP unless waiver or deferral.

This new legislation makes paediatric development an obligation in the EU, with the following key points:

- Creation of a European Paediatric Committee (PDCO) (July 2007).
- Submission of Paediatric Investigation Plan at availability of adult pharmacokinetic studies, i.e. at an early phase of the development of a new compound.
- Paediatric data is mandatory for all regulatory submissions for new products and for products still on patent in case of line extension (unless waivers or deferrals) according to a PIP agreed upon by the PDCO.
- PIP reflects the development plan on clinical, non-clinical and technical aspects including timelines and covers all existing or planned (adult) indications and dosage forms (including specific paediatric formulation if necessary).
- PIP can be amended and is binding on the company.
- Reward for studies conducted can result in a 6-months patent extension.

Discussion

Since the therapeutic effects of amphetamines in hyperactive children were first described in 1937, preceding the major discoveries of adult psychopharmacology, little innovation has occurred in paediatric psychopharmacology (Vitiello 2007). Furthermore, while progress in the recognition and treatment of mental disorders in childhood and adolescence has been accomplished, the task of turning basic research findings into clinically useful applications still remains in front of us (Fegert and Vitiello 2007).

Actually, only few psychotropic medications are approved for use in the paediatric population. However, it has become increasingly common to use these medications to treat a variety of mental health disorders in children and adolescents but this has not constantly been supported by rigorous scientific data. A study of the prescribing trends in nine countries between the years 2000 and 2002 evidenced that the increase in psychotropic prescribing in children was not only confined in the USA and UK but is also evident in the 7 other examined countries (Argentina, Brazil, Canada, France, Germany, Mexico, and Spain) (Wong et al. 2004).

The questions related to the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in Paediatric Major Depressive Disorder (MDD) can provide an opportunistic example of where paediatric pharmaceutical research can improve. The official

recognition of depression in children and adolescents in Europe took place in 1971, when the Union of European Pedopsychiatrists recognised and addressed the needs of depressed children and adolescents by declaring that depression is an important illness that constitutes a significant proportion of mental disorders in children and adolescents (Weller et al. 2004). During the 1980s, the arrival of the SSRIs, which resulted in far less side effects than tricyclics or monoamine oxidase inhibitors, was viewed as an important step in the treatment of affective disorders, first in adults and then in children and adolescents (Cohen 2007). Simultaneously, the literature on the treatment of MDD in children and adolescents has significantly grown since the introduction of the SSRIs. Although the exact mechanism of action responsible for the therapeutic effects of many psychotropics remains unknown, the basic biochemical activity of these medications is generally considered to be similar across all ages (Vitiello 2008). In both paediatric and adult patients, SSRIs block the reuptake of serotonin and their antidepressant effect has been found to be associated with the degree of inhibition of the serotonin transporter in platelets (Axelson et al. 2005). However, it still remains to be proven whether SSRIs that are efficacious in adults are also efficacious in treating MDD in children and adolescents (Moreno et al. 2007). Most of the clinical studies did not demonstrate superiority of active treatment when compared to placebo as: only fluoxetine was repetitively superior to placebo on primary outcome measures; studies of citalopram, sertraline and escitalopram recently (Emslie et al. 2008) have also shown superiority over placebo on primary outcome measures; studies of paroxetine, venlafaxine, mirtazapine, nefazodone, and tricyclics have not demonstrated superiority of any of these pharmacological treatments over placebo on the primary efficacy measures (Cohen 2007; Wagner 2005; Moreno et al. 2006; Usala et al. 2008). At present, only fluoxetine is approved in EU and US for paediatric MDD.

The reasons why many of these studies have failed remains unclear. Although some of these antidepressants may not be beneficial (like probably tricyclics), methodological considerations have been raised, among them dosing issues should be carefully evaluated. Extrapolation from adult data is definitively insufficient. Some authors hypothesized that inaccurate dosing parameters may have participated in the negative outcome of the studies of antidepressants in paediatric patients with MDD (Findling et al. 2006).

Key parameters of dosing that should be evaluated include identifying an appropriate total daily dose and determining how frequently the medication needs to be administered every day. If a medication is not dosed properly, clinical efficacy might not be detected during a clinical trial (Findling et al. 2006). The selection of doses in paediatric patients requires a consideration of pharmacokinetic parameters and warrants specific studies in children and adolescents to establish benefits and risks during drug development (Atuah et al. 2004), deemed as a pivotal aspect of paediatric drug development. Reviewing the pharmacokinetic (PK) studies performed in children and adolescents with SSRIs, R. Findling et al. in 2006 concluded that in many instances, the dosing strategies that have been employed in the placebo-controlled efficacy studies in juvenile MDD were not supported by the data available from PK studies (Findling et al. 2006). Therefore, these authors emphasize the need to develop evidence-based dosing strategies before studying any drug in paediatric population as medication dosing regimens may have contributed to both failure to demonstrate efficacy and safety and tolerability concerns (Findling et al. 2006). Reviewing the paediatric randomized controlled MDD trials, Moreno et al. reached a similar conclusion: as antidepressants have two to three times shorter half-lives in youngsters, they need to be administered more often than to adults to avoid withdrawal symptoms between doses that can be wrongly interpreted as the absence of an adequate response with the exception of fluoxetine, which has a longer half-life (Moreno et al. 2007). Consequently PK and dose ranging studies are needed to inform the design of definitive efficacy trials. But such type of paediatric studies remain difficult to perform and alternatives like modeling are developed as they are ethically challenging mainly due to the fact that such research does not offer a prospect of direct benefit.

What occurred since the new EU Paediatric Regulation had entered into force can be seen as an ongoing learning process. Contrary to what has happened in the US, the EU paediatric legislation is leading to more dramatic and faster changes in a still moving and complex environment. The legislation entered into force in January 2007, the PDCO first met in July 2007, and one year after entering into force, the Commission Guideline on format and content of Paediatric Investigation Plan was on a draft format implying that all stakeholders will have to work together and interact to overcome the challenges of this new regulation. Numerous aspects of this new process will lead to interesting interactions and future developments.

The EU paediatric legislation does not make any difference between products already on the market and drugs in development. The transition period does not allow enough flexibility to take into account specific product patent timelines meaning that paediatric development may not be possible for some products still on patent. It is too early to draw any clear conclusion but the fact that after one year almost two thirds of the applications are for medicines that are not yet authorised (PDCO first anniversary) seems to be in favour of this concern. It could be wished that for new products, there would be more opportunities to interact with the PDCO. The example of atomoxetine development can be useful, as it has heavily been influenced by US paediatric regulation and guidance from the FDA, also showing that new and integrated adult and paediatric models can be achieved (Allen and Michelson 2002). Therefore, it could be of interest to offer further opportunities of direct interactions between the PDCO and the Pharmaceutical Companies as improving the communication around the common goal to develop better medicines for children between the PDCO and the Pharmaceutical Companies can only be beneficial.

More emphasis on integrated paediatric and adult development could have eventually been suggested in the Commission Guideline. The timing of PIP submission offers for instance a possibility of debate as one can consider that the end of adult PK studies does not necessary mean end of phase I.

The EMEA guidelines for psychiatric conditions will need to be revised with specific paediatric considerations. These guidelines provide already some clear guidance as they confirm the existence of numerous paediatric conditions in different age groups (according to ICH E 11 (ICH 2004)) but the methodological sections lack of paediatric specificities. The first paediatric EMEA guideline under development will be for ADHD and should offer an integrated adult/paediatric development.

Two specific aspects can illustrate this question such as the use of placebo in children and adolescents and the question of comorbidity. If from a scientific point of view, randomised double-blind comparisons versus placebo are often preferable to permit adequate evaluation of efficacy and safety/tolerability, the use of placebo raises ethical concerns potentially leading to different opinions between Health Authorities and Ethics Committees. Ethical requirements must be taken into consideration when designing paediatric protocols and PIPs and paediatric

protocols cannot simply be mimic adult protocols. For instance, rescue treatment and escape procedures should always be considered in paediatric trials: rescue refers to treatment that may be given on top of trial medications to avoid danger or distress, for example pain treatment, as soon as the patient reaches a defined level; escape refers to prompt removal of subjects whose clinical status worsens or fails to improve to a defined level in a trial (European Commission 2008).

Comorbidity is not accepted in the current EMEA guidelines, and the patients to be included in the trials should have only one specific disease (e.g. patients with MDD and with no anxiety disorders). However, it is well established in child and adolescent psychiatry that comorbidity is the rule rather than the exception (Caron and Rutter 1991): clinical and epidemiological investigations have revealed that 40%–70% of depressed children and adolescents have comorbid psychiatric disorders and that at least 20%–50% have two or more comorbid diagnoses (Weller et al. 2004).

Compared to the US, the EU experience in paediatric research is less extensive. In the field of child and adolescent psychopharmacology, the majority of publications and studies are coming from the US. Reviewing 27 placebo-controlled trials assessing the use of antidepressant medications among more than 4,400 children and adolescents published between January 1998 and July 2006 in Medline, Apter et al. reported that 23 out of 27 were conducted solely in the US and only 3 were done partly in European countries (Apter et al. 2007). This new legislation will help developing an EU network of potential investigators in child and adolescent psychiatry, emphasizing that identification and training of new research centers will also have to take place. However, it will be necessary to take into account the public perception of paediatric research in Europe and the awareness of Ethics Committees. Currently, the European Commission's Guideline on the PIP does not take into account feasibility issues. If this is understandable, such feasibility potential issues or concerns will be translated to facts e.g. geographic localisation of the study when the first studies part of the PIPs will be recruiting and may lead to PIPs amendments.

Another major challenge will be to ensure as much as possible global paediatric development mainly for EU and US (keeping however in mind that other countries are also following this path of paediatric legislation), working ideally on common study designs in order to avoid unnecessary duplication of studies and expose children to undue risks. As a possible start towards global paediatric development, an

option could be to develop a common process between FDA and EMEA in order to make Pediatric Written Requests and Paediatric Investigation Plans compatible.

Finally, the financial aspect of paediatric development cannot be eluded and its impact on pharmaceutical companies will have to be assessed. In 2007, before the US paediatric legislation was renewed, Li et al. examined the returns on investment of completing paediatric exclusivity and demonstrated that the distribution of net economic return for six months of exclusivity varied substantially among products, being very positive for blockbusters but being also potentially negative in some cases. They concluded that the Pediatric Exclusivity Program overcompensates blockbuster products for performing clinical trials in children. There is a concern that if paediatric development is more difficult and expensive than anticipated, what could be the potential risk on research in Europe for primarily EU companies, especially for small or medium size companies?

Conclusions

The European Paediatric Regulation is a major achievement and opens a new era of European drug regulatory history. Children have often been denied access to new or innovative medications and paediatric development still depends on the outcome of the adult development. This regulation offers a major opportunity to improve children's health. But, paediatric development remains challenging and the hurdles of conducting research in paediatric population are numerous including 'moral' and ethical issues, scientific issues, practical issues and finally financial issues. Therefore as a shared responsibility among companies, regulatory authorities, health professionals, and society as a whole (ICH E-11), it is through the lessons learned during the implementation of this new legislation and the numerous dialogues that will result, that changes will occur, promoting paediatric research. Ultimately, it is through well-conducted ethical and quality research that children and adolescents will gain access to new medications and receive safe and optimal drug therapy.

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