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Berlin, 31th of August 2016

## **Ethical Considerations for Clinical Trials conducted with Minors**

Dear recipients of this contribution,

the Relief Center for Evangelical Pastors (Hilfsstelle für ev. Pfarrer, website: [hilfsstelle.de](http://hilfsstelle.de)) is supporting theologians in helping others in need and is supported itself by the German Evangelical Pastors' Union (Verband der Evangelischen Pfarrerinnen und Pfarrer in Deutschland, website: [pfarrverband.de](http://pfarrverband.de)) to which nearly all Lutheran and Reformed Pastors of the former protestant statechurches belong.

We would like to draw the European Commission's attention to some ethical and also judicial aspects concerning clinical studies in common and clinical child-studies in particular, although those aspects were not mentioned in the (unofficial) paper or draft the public was asked to react on and to contribute to.

We think those further ethical issues must be discussed, whenever we talk about ethics in the context of clinical trial or medical experiments on human beings. For those ethical conflicts we would like to draw your attention to are concerning questions of life and death and the right of third persons to decide about others' life or death.

If this question is not seen clearly as the first and the main ethical (and may be also judicial) question concerning clinical studies, all improvements in minor aspects can only hide the main problem and the fact that we fail to improve the answers to this question.

In the present, you get by responsible persons only answers like: „If you want to get scientific relevant results, please cut off your feelings“ „Those ones (inside or outside a study) you now care

for have to die now because if they die we can get earlier valid results and can help lots of others earlier as if we would help them now to survive.“

In the last years we have got a very loud discussion about this question in the German media. Especially the parents of children with rare or „orphan“ diseases mobilized several journalists and also a big interested public. This happened in German neighbour-countries (like perhaps Poland), too.

As far as we see, there are three cases, when patients or parents mean that their children or they themselves are sentenced to death by the sponsors of a clinical trial:

1. The study design is such narrow, that they cannot enroll (they're not fitting in the profiles or enrolling is already closed)
2. The study design is with placebo arm and the primary endpoint is defined by the death of a significant number of those ones in this arm.
3. Although this would be legal, the studies sponsor refuses „compassionate use“ or other legal ways to give the compound outside the study for to save the lifes of those children that couldn't wait for the end of the study and the market access.

The anger about these three cases in German public is very high. But medical doctors and scientifics think, the stupid people doesn't understand what is necessary.

In this situation, our institution decided that it could be interesting to know about what first of all the lawyers say from an iudicial point of view, and when we see clear in this point, then to ask the ethicist (like us theologicans, but also other ones) and last but not least politicians.

On the 11th of February 2016 our relief center published an invitation for tender for a legal opinion according to the subject „New drugs for whom and when?“ (both, the German text and the English version you find attached).

The legal expert opinion we asked for was made by Prof. Dr. Stefan Huster, Dr. Stefan Stadelhoff (Ruhr Universität Bochum) and Dr. Anne Streng-Baumann an completed in the end of July 2016.

Some leading German media like „Süddeutsche Zeitung“ or „Der Spiegel“ (those articles also attached here) wrote about this legal opinion and the questions it could be important for. Until today, the 31th of August 2016, Prof. Huster's legal opinion isn't published yet, but if the European Commission is interested, we could leave it a copy of the (only) German version (about 100 pages including the summary).

In this contribution we hope it would be enough to mention the ethical regards remaining still important after getting the answers to the legal questions first.

**The following considerations are regarding the case that a clinical trial is made with a new compound and there is still no sufficient standard of care existing and the compound as seen already in phase 2 seems to be working life-saving so that getting the new compound in- or outside the study could decide over life and death. This means, it is regarding mainly orphan diseases. And this means, the consideration are regarding mainly clinical trials conducted with minors.**

1. Defining who's inside or outside the study could be an ethical problem, when the decider doesn't take care that anyone needing the compound could get it outside the study, too, where legal ways exist.
2. Giving the compound to anyone who needs it outside the study could be an ethical problem if the study is designed with a placebo-arm.
3. This could also become an economic problem: „Giving patients access to experimental drugs could also discourage them from enrolling in controlled trials that might assign a placebo, and would leave less drug available for use in the trial.“ (Sara Reardon, Panel tackles ‚compassionate use‘, Nature Volume 534, June 2016, page 160 f, here also attached)
4. Forcing people to enroll in studies by refusing the outside access to experimental drugs, though it would be legal and possible, is – according to the criminal law in Germany - no juridical problem. But it could perhaps be a juridical problem according to the German civil law (both is the result of the legal opinion by Prof. Huster).
5. Continuing a placebo designed study to its designed primary end point could be a legal problem according to the German national criminal law, when the advantage of the verum against the placebo is clear enough before reaching it (also in result of the legal opinion of Prof. Huster).
6. If this point is met in the view of the study's sponsor but the EMA indicates that the study has to continue because the advantage may be clear, but not clear enough for getting the approval already, we've got one more ethical and perhaps juridical problem (in one of the cases discussed in our invitation for tender, this obviously happened and the EMA retarded compassionate use for several months).
7. In a mathematical or scientific view, it is clear that you won't get the same evidence by a study with only 23 probands like often at rare diseases as by a study for popular diseases with minimum 1,000. The scientific question is: Can this lack of evidence really be improved by a placebo arm? Depending on the scientific answer by which factor this could improve the evidence, we get to the ethical question how many lives this (senseful or probably senseless) improvement may cost – inside and outside the study (if you consider that compassionate

use is normally refused as long as the placebo arm is going on).

8. There is one usual possibility to renounce completely a placebo controlled phase 3 in a study, namely if it were not possible or if there would be a high medical risks if you decept a donation of the compound (like in one oft he cases discussed in our invitation for tender). But the fact, that the death of a significant number of members oft he placebo group is not only risked, but defined as the primary endpoint oft he study and will surely be reached is no reason to suspend it? This is one time more an ethical problem as outside the study with the same necessity lots of children will die at the same time because they won't get the verum, too, while the placebo study is ongoing (for not to risk that there won't be enough interested probands in the future).
9. One more reason to renounce completely a placebo controlled phase 3 study could also be if there were enough natural history dates about a disease. This was the case in both oft he mainly discussed cases, but only in one case this was taken as one more argument to renounce a placebo group, obviously because the EMA saw (in contradiction to other experts) not enough evidence. One possible technical solution for this ehtical problem could be an improved register for rare diseases for to collect natural history data and EU-supported projects. But the register was already intended by the EU and opposed by the German protestant church because of the fear of a genetical selection or discrimination – but not considering how the lifes of placebo probands and compassionate use searching children outside a study would suffer from this fear. There should be a new ethical discussion about the register considering this relation.
10. When after finishing a study compassionate use is really made, there still is the question: When and who will get access and who not an who will select those ones? The legal expert opinion made by Prof. Huster and others mentions this case as an example where the German civil law could perhaps force the access for excluded persons if there are not transparent reasons for their exclusion. But the fear is still ongoing that the private autonomy of medical companies could give them the possibility to designe the conditions for compassionate use in a way that critics could be punished by excluding their children or that contracts could be made that have to be signed before taking part in compassionate use that would lead to a penalty for non performace if their former critic will be repeated by anyone else (in one case that was discussed in our invitation for tender, this fear against the nearly allmighty life and death deciding pharmaceutical industry lead to really tragical and expensive consequences).
11. If there are improvements consicered for the ethical questiosn 1 to 10, the commission has to consider to make them not only for studies made in Europe but also for studies made

outside of Europe if they should cause any European market access. This were possible by defining them as ethical standards for a Good Clinical Practice. Otherwise people in countries with lower ethical standards could become the guinea pigs for Europe. Furthermore if a study for one and the same compound is made in several countries inside and outside of Europe, compassionate use should start at all places at the same time, if this is legal there. In an ethical view, one life of a child is worth as much in Germany as in Ankara or Hong Kong (In one case discussed in our invitation for tender this simultaneous event is probably missed by unknown reasons).

We would be lucky if the European Commission could take this ethical and juridicial hints in consideration and look forward for improvements also concerning these issues.

With kind regards



Pastor Christian Johnsen,

Leader of the Relief Center for Evangelical Pastors, Berlin

**Attachments:**

Hilfsstelle für ev. Pfarrer, New Drugs for Whom and When? Inviation for tender for a legal opinion, 11th of February 2016 (English and German version)

Christina Berndt, Vom Recht auf Leben, SZ 5th of March 2016, page 10

Sara Reardon, Panel tackles ‚compassionate use‘, Nature Vol. 534, 9th of June 2016, page 160f

Viviane Pasquet, Diagnose ohne Mitgefühl, Spiegel Nr. 31/2016, 29th of July 2016, page 106ff

# New drugs for whom and when?

## Invitation for tender for a legal opinion

(In the case of any doubt with this translation, please refer to the German original).

The Relief Centre for Evangelical Pastors (registered society) is an association for the support of theologians supporting those affected or personally affected by bullying, transfer, dismissal, lay-off, burnout, illness, disability, discrimination, arbitrary justice or political persecution. One of its statutes is to counteract arbitrary administration of justice in and outside the Church, and thus to contribute to the preservation of the free and democratic constitutional state.

In the 20th year since its founding, the centre wants to commission an assessment on issues of pharmaceutical law. It is a matter of human lives, which are potentially dependent upon the legal situation of all involved parties being correctly assessed, in that window of time in which the new drugs are being developed, but not yet approved. If there are already serious indications that life threatening diseases can be successfully treated with these substances, who may receive them and under which circumstances, who may not, and who should decide?

In the literature and commentary, indications can be found that the German legal situation is contradictory, with dire consequences. 2005 and 2009 updates of the Medicines Act (AMG) were criticized by specialist lawyers, that the legislature had created a legislation contrary to constitutional and European law, one which would cost lives.

In fact, in the years after that, reports appeared in the media of tragic individual cases, where parents struggled vainly to obtain such drugs for their children. A comparison with other European countries also shows that our neighbours sometimes make such drugs available 5 or 6 months earlier - months, which can make the difference between life and death. There is also a double placebo effect: where there is no standard, but a new drug works, not only do the study participants in the control group go empty-handed, but also all non-participants, for they should not be placed in a better position.

An analysis should therefore first clarify how far the legislation disputed in the literature is responsible for those tragedies. For this purpose, the Relief Centre has compiled 10 key questions and an explanatory text with facts, arguments and evidence from the discussion so far and published them on [hilfsstelle.de](http://hilfsstelle.de). It means to support colleagues who care for affected families, and also sensitize other theologians who decide in ethics committees over pharmaceutical studies or who are in dialogue with citizens, professionals or politicians.

Interested lawyers are requested to estimate the costs and to please send a bid by 15th March 2016 with a fixed price, the latest completion date and references (if applicable under disclosure of links to the pharmaceutical industry) to the:

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## Key Questions

Invitation to tender for a legal opinion on the following questions issued by the Relief Centre for Evangelical Pastors:

1. whether the refusal by a pharmaceutical company, to make an as yet unapproved drug available for an individual therapeutic trial according to § 21 II 6 AMG (new version) i.c.w. § 1 AMHV, is criminal by public law, being failure to render assistance pursuant to § 323c of the German Criminal Code or, conversely, whether the issue of the medication, if required neither by law nor making economic sense, according to domestic or foreign law as a breach of trust within the meaning of § 266 of the Criminal Code be punishable and can trigger a mandatory recourse against the responsible decision-makers.
2. whether the same refusal moreover, may be punishable as assault under § 240 of the Criminal Code if the organisation does so with the ambition of forcing persons seeking a cure to participate in controlled studies that it could not otherwise recruit.
3. whether the allocation of subjects to a placebo group is a de facto crime such as assault or homicide if as a result this progredient disease is left untreated.
4. whether in the case of an adult, consent to participate in controlled studies comprises justification for allocation to a placebo group, when in so far based on insufficient clarification, as the study-leadership have either not informed subjects of the legally available alternative of an individual therapeutic trial or Compassionate Use with the medication or because such clarification could only therefore be avoided, because the commissioning pharmaceutical company thwarted these alternatives by de facto refusal, giving no alternative but for study participation for treatment seekers.
5. whether in the case of minors, a purely group-specific benefit in accordance with § 41 AMG can ever be justification or whether this legal provision has been unconstitutional ever since its introduction in 2005 and therefore in analogy with the jurisprudence of the ECtHR on the "shoot to kill" policy, even as "applicable law", cannot legitimise the right to physical integrity or the right to life.
6. whether § 41 AMG, even when unconstitutional, leaves those responsible exempt from punishment, because the provision generated by the fiction of a group-specific benefit as justification creates an unavoidable mistake of law within the meaning of § 17 clause 1 of the Criminal Code and by this error in extreme cases, may act as a "license to kill" (negligent or deliberate) or would in turn be put down to the judgement of the supreme court to "shooting order" of the former GDR.
7. whether the endorsement of a study by the competent ethics committee, in the designated or other cases, under certain circumstances can mean complicity.
8. whether one of the offences described under 1-3, causing damage to life or health, would result in claims for damages according to § 283 BGB against a pharmaceutical company.
9. whether the refusal described under 1, if punishable as a failure to render assistance, could be overcome by court order and, if so, by which process route.
10. whether this means the state should take legislative action as part of its duty of protection and whether, if it fails to take appropriate initiatives to remedy the situation, proceedings can be initiated against the Federal Minister of Health on the basis of a guarantee due to the crime of endangerment or due to consummate negligent bodily harm or killing. As was already attempted against Ulla Schmidt in 2004.

## Explanatory text

### ***Individual therapy trials and "Compassionate Use": the theory***

In 2005, the German legislature introduced, through the 14th amendment to the German Medicines Act (AMG), some innovations that follow European rules.

Since then, the new version of § 21 AMG in conjunction with Article 83 of Regulation (EC) no. 726/2004 permits the use of not licensed medicines in the context of so-called "Compassionate Use" (CU), when *"they are provided for use in patients, who are suffering from a disease leading to severe disability or whose disease is life-threatening, and who can not be treated satisfactorily by an authorized medicinal product."* (§ 21 clause 2 no. 6 AMG N.F.).

In practice, the new version only became effective on 15<sup>th</sup> July 2010 with the introduction of the Drug Hardship Regulation (AMHV), immediately preceding which the legislature added the word "free of charge" at the beginning of the sentence just quoted. (Bundestag printed paper 16/12256 from 16<sup>th</sup> March 2009, pg.15)

<http://dipbt.bundestag.de/dip21/btd/16/122/1612256.pdf>

Individual therapy trials continue to be permitted in such cases alongside Compassionate Use Programs. The difference lies in the fact that in individual therapy trials the medication is provided to a single doctor, in each case, for the treatment of a limited number of patients under his responsibility without a government agency having to be involved (§ 1, clause 1 AMHV), while a Compassionate Use Program has to go through the entire approval procedure of the remaining provisions of the AMHV.

[https://www.vention.de/gesetze/Gesetzestexte/AM\\_Haerterfall\\_VO.html?mainPage=1](https://www.vention.de/gesetze/Gesetzestexte/AM_Haerterfall_VO.html?mainPage=1)

<http://www.juraforum.de/gesetze/amg/21-zulassungspflicht>

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20090706:DE:PDF>

Based on majority opinion a state of emergency in accordance with § 34 of the Criminal Code must be remedied (such as Adem Koyuncu, Karsten Fehn, Catia Meyer, "The criminal justification of individual therapy trials and the relationship of § 34 of the Criminal Code to § 21 clause 2 no. 6 AMG" , PharmR 2014 91-98).

<http://www.brainguide.de/Die-strafrechtliche-Rechtfertigung-individueller-Heilversuche-und-das-Verhaeltnis-von-34-StGB-zu-21-Abs-2-Nr-6-AMG>

The justification of the amendment, on the other hand, sounds as if it would contain a new legal basis for just these common cases:

*"According to current law new drugs remain unavailable to patients up to their approval, except in the context of a clinical trial or a provision relating to a justifiable emergency. Henceforward the legal conditions will be created for the provision of such medicinal products"*(see Bundestag printed paper. 15/5316 Pg. 36).

<http://dip21.bundestag.de/doc/btd/15/053/1505316.pdf>

In any case, at least since then there have been two legal ways to gain access to such medication outside of clinical studies. (see. Fabian Huber's dissertation of 2014 "Individual healing trial and clinical experiment")

<http://d-nb.info/1077705824/34>

Next to the standardisation of the law, the European guidelines' goal was pre-approval achievement "*particularly corresponding with the legitimate expectations of patients and the increasingly rapid progress of science and therapies*", to be reached through accelerated authorization procedures in justified cases and standards for compassionate use.

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20090706:DE:PDF>

## **The practice: Pharma companies deny life-saving assistance**

However, in practice this does not work, at least not in Germany. Here few companies provide their drugs for compassionate use programs. The body responsible for approvals, the Federal Institute for Drugs and Medical Devices (BfArM), at the end of 2015, lists only 14 ongoing programs by pharmaceutical companies (in France in 2007 there were more than ten times as many, see below).

[http://www.bfarm.de/DE/Arzneimittel/zul/klinPr/compUse/Tabelle/\\_node.html;jsessionid=922E9BF585D1F07C2B2BA9EBC9549076.1\\_cid350](http://www.bfarm.de/DE/Arzneimittel/zul/klinPr/compUse/Tabelle/_node.html;jsessionid=922E9BF585D1F07C2B2BA9EBC9549076.1_cid350)

Many pharmaceutical companies even refuse to provide their medication upon the request of a doctor who accepts the responsibility for individual therapy trials.

This is not always different in other countries. Worldwide, specialized pharmaceutical companies are not only making headlines with their successes in the fight against rare diseases, but also due to people whom they have simultaneously and mercilessly permitted to die.

Legal history was made in the United States on 1<sup>st</sup> January 2014 by the lawyer Andrea Sloan from Austin (Texas) when, after a long struggle against the company BioMarin for the administration of a cancer healing drug, her death instigated a new law.

<http://kxan.com/2015/02/23/andrea-sloan-right-to-try-legislation-filed-in-texas-senate/>

In 2013 in the UK, the death of 17 year old Chloe Drury aroused similar attention. Chloe was just a few months too young to get the, for her, lifesaving drug from BioMarin, because it had hitherto been tested only on adults.

<http://www.tributeslides.com/tributes/show/QKKXBTHX62JN5K3L>

In Germany in 2015 two doomed children with rare diseases have been the main ones to arouse public media attention: Hannah Vogel from Greiling near Bad Toelz and Miguel Morales-Laubinger from Hildesheim.

Since May the ARD, ZDF, Die Welt and the SZ, inter alia, have reported upon 10 year old Hannah, who suffers from child dementia (NCL2) and whose doctor did not receive the medication necessary from BioMarin for her salvation.

<https://www.freitag.de/autoren/christianberlin/lebensretter-oder-killerkonzern>

Neither the online petition #savehannah, now at year's end with almost 400,000 signatures, nor discussions between Hannah's parents and representatives of BioMarin or politicians could change anything so far.

<https://www.change.org/p/bitte-helft-unserer-tochter-hannah-9-jahre-alt-zu-leben-savehannah>

Since July, the HAZ and Bild reported upon Miguel Morales-Laubinger, almost two years old, who suffers from spinal muscular atrophy (SMA) and is not expected to survive the next two years.

<https://www.facebook.com/photo.php?fbid=1650853685127009&set=a.1396678660544514.1073741833.100006071800190&type=3&theater>

Finally in November a doctor requested the,for Miguel, presumably lifesaving medication SMNRx, via Biogen at ISIS Pharmaceuticals (since 18 December renamed "IONIS Pharmaceuticals"), for an individual therapeutic trial and received a similar rebuff as for Hannah at BioMarin. *"Biogen currently has no compassionate use program for ISIS-SMA Rx (sic!), i.e. treatment with ISIS SMNRx is limited at the present time to patients who participate in clinical studies. ... those studies currently recruiting patients, are the following: ..."* (release dated 24<sup>th</sup> November 2015).

Both children are still alive and can, in the opinion of their doctors and parents, be saved if they were, for an individual therapeutic trial, to receive respectively SMNRx from ISIS Pharmaceuticals and Cerliponase Alfa (BMN 190) from BioMarin - provided that the two organisation's messages on the successes achieved on 12<sup>th</sup> January 2015 or 11<sup>th</sup> June and 17<sup>th</sup> October 2015 respectively, are correct.

<http://investors.bmrn.com/releasedetail.cfm?ReleaseID=890846>

<http://www.biomarin.com/products/pipeline/cerliponase-alfa-bmn-190-tpp1-for-cln2-disease/>

<http://smanewstoday.com/2014/10/17/isis-smn-rx-shows-efficacy-in-infants-with-sma-during-phase-2-studies/>

The success of Cerliponase Alfa was made known in Germany by the ZDF program People – The Magazine on 18<sup>th</sup> April 2015, in which the mother of 5 year old Sara Kanitz, who has been participating in the study since 2013, said: *"It is often ambivalent. So I'm happy that we are involved ,and because it's just going so well, I think of course also of the others who can not participate. That is what one would wish for every child, that it runs as it currently is doing."*

<http://www.zdf.de/ZDF/zdfportal/programdata/678a15b0-9776-3996-9d56-49ce8a03c5cf/20427190>

## The grounds for the refusal

The reason manufacturers of such medications give to not comply, to run no compassionate use program and to refuse provision for individual therapeutic trials is always the same:

BioMarin: *"We do not want to endanger the development of Cerliponase Alfa, from which - if the therapy is successful - hundreds of patients and their families can profit"* (from a Media Statement by BioMarin on 5th May 2015).

<https://www.freitag.de/autoren/christianberlin/lebensretter-oder-killerkonzern>

Biogen/ISIS: *"Making our drug available earlier in the process could jeopardize potential approval and ultimately access for patients around the world."* (From an undated statement from Biogen and ISIS Pharmaceuticals from November 2015 to the members of the SMA community, available to the Relief Centre)

Surprisingly the Alliance for Chronic and Rare Diseases (ACHSE) uses the same argument against individual therapeutic trials:

ACHSE: *"It does not help when, during a clinical development, a drug is given prematurely and uncontrolled, through which the whole clinical development may possibly be endangered and leading to all patients who have this disease, receiving the medication either much later or not at all"* (Statement to camera by Dr. Andreas Reimann as chairman of ACHSE in the ZDF broadcast "Mona Lisa", broadcast on 23<sup>rd</sup> May 2015).

<http://www.zdf.de/ml-mona-lisa/ncl2-kinderdemenz-der-streit-um-den-heilversuch-38573524.html>

Assuming these similarly worded statements are credible, they immediately raise a fundamental question of legal principle:

Is it permissible in this fashion to weigh individual and third party benefits against each other when it comes to life and death? Or is that a "relativism of the right to life" as clearly rejected by the Federal Constitutional Court in a judgement on the shooting down of an airplane on 15<sup>th</sup> February 2006 (1 BvR 357/05)?

[http://www.bundesverfassungsgericht.de/SharedDocs/Entscheidungen/DE/2006/02/rs20060215\\_1\\_bvr035705.html](http://www.bundesverfassungsgericht.de/SharedDocs/Entscheidungen/DE/2006/02/rs20060215_1_bvr035705.html)

This judgement shows at least: the maxim of forfeiting an individual life in the present, in order to improve the chances of saving even more lives in the future, could - even if erroneously assumed by politicians - never be the basis of a universal legislation in a liberal constitutional state. That's why it was and is, following the categorical imperative, to be assessed as unethical.

If the pharmaceutical companies' and ACHSE's argument cannot legitimize the refusal, then the refusal is unjustified. Whether it is then permissible depends upon the question of whether they can be subsumed under criminal law as a prohibited act.

## Legally permitted and legally offered rescue attempts

This is supported by a very strong argument: The premises of §§ 32 (self-defence) or 34 (justifiable emergency) and 323c of the Criminal Code (failure to render assistance) are almost identical.

*"If the emergency aid, a legally allowable (§ 32, see also § 34) or offered (§ 323c) rescue attempt, is a legal right, therefore not attempting or offering it is criminal failure and damages the legal right"* (Leipziger Kommentar on the Criminal Code Vol. VII, to § 323c Rn 21)

<https://books.google.de/books?id=-q3yCQAAQBAJ&printsec=frontcover&hl=de>

The word "or" in the preceding set of conditions between "allowable" and "offered" means that one of the two alternatives may be sufficient to render unlawful a non-observance of rescue opportunities. This should especially be the case if a guarantor situation exists as with a doctor, with a contract for treatment.

Courts decide on a regular basis in such cases, that a physician by such omission, makes a per se prohibited, but justified offence, according to § 34, and is obliged to pay damages.

The Frankfurt Higher Regional Court had, on 5<sup>th</sup> October 1999, to judge upon the case of a doctor treating a patient infected with HIV, and his partner who, according to the infected person, should not be informed of the illness.

*"In its judgement the Higher Regional Court (OLG) emphasised that patients with HIV or AIDS must be protected in their trust in the reliability of medical discretion (§ 203 Criminal Code). However, this principle is restricted by § 34 of the Criminal Code. According to which the medical code of privacy may and should be broken to protect a more significant legal interest".*

<http://www.aerzteblatt.de/archiv/22540>

However, in this case the doctor escaped liability because a court expert considered it likely that the partner had been infected before the diagnosis.

On 30<sup>th</sup> May 1990 the Cologne Higher Regional Court sentenced a clinic to compensation for permanent damage because their doctors used the as yet unapproved drug Acyclovir in an Off-Label Use, not immediately upon suspicion but only after the confirmed diagnosis and thus at least 24 hours too late (27 U 169/89).

The OLG joined the applicant in the appeal, who was of the opinion, "the then lack of approval of acyclovir for herpes encephalitis should not have stood in the way of its use. It should, on the contrary, have been absolutely necessary according to medical knowledge to use this remedy immediately upon suspicion of the disease, because this was the only promising therapy. Adverse side effects were not to be feared."

<https://openjur.de/u/443491.html>

But is there such a commitment when there is no treatment contract, if perhaps a doctor just happened to be nearby when a child had a seizure, he had the medication with him or was able to acquire the medication with his medical card from a nearby pharmacy, the way to the hospital was long and every minute had counted?

If so, then whenever they are medically possible and legally permissible, individual therapy trials would be obligated by law.

The first person who carefully examined this question, was Adem Koyuncu. Together with his co-authors, in the aforementioned essay *"The justification in criminal law for individual therapeutic trials and the relationship of § 34 of the Criminal Code to § 21 passage 2 no. 6 AMG"* (PharmR 2014, 91-98), they reached however a contrary conclusion.

<http://www.brainguide.de/Die-strafrechtliche-Rechtfertigung-individueller-Heilversuche-und-das-Verhaeltnis-von-34-StGB-zu-21-Abs-2-Nr-6-AMG>

Koyuncu bases his argument on the fact that a commitment to emergency assistance results from § 323c only if they can "under the circumstances reasonably be expected, in particular without substantial risk to themselves and without violating other important duties". He is of the opinion that the de facto offence, even when not against the law, while justified by § 34, constitutes a violation of important duties and therefore can not be expected.

Koyuncu's result is unsatisfactory especially because it can not be right. Even alone the aforementioned higher court judgements refute his argument. The law does not allow, in offences relating to failure to act, the accused the excuse or justification that the failure to act would have solely been legal through § 34, per se forbidden and therefore unreasonable. And that is not just because of the doctor's guarantor role.

Already on 26<sup>th</sup> October 1982 the German Federal High Court sentenced a doctor, not under contractual obligation, for failure to provide assistance, on the grounds that he had complied with the Hippocratic code of privacy, even though breaking the oath could have saved a person's life and been so justified by § 34 (1 StR 413/82).

[https://books.google.de/books?id=g\\_gBYozq5oC&pg=PA44&lpg=PA44&dq=BGH+vom+26.10.1982+%221+StR+413/82%22+#v=onepage&q=BGH%20vom%2026.10.1982%20%221%20StR%20413%20F82%22&f=false](https://books.google.de/books?id=g_gBYozq5oC&pg=PA44&lpg=PA44&dq=BGH+vom+26.10.1982+%221+StR+413/82%22+#v=onepage&q=BGH%20vom%2026.10.1982%20%221%20StR%20413%20F82%22&f=false)

The state prosecutor wanted to prosecute for homicide but this was rejected by the German Supreme Court.

*"The lower court has therefore dissociated itself from a conviction for manslaughter, because it could not be proven that the accused was under contractual obligation. He was contracted by the mutual contractual parties solely for consultation pursuant to § 218b of the Criminal Code and had neither wanted nor commenced medical treatment ... These findings are binding on the Court of Appeals."*

Likewise, the German Supreme Court upheld the lower court of Rottweil's decision against the accused's appeal attack:

*"The conviction for failure to provide assistance is supported by the findings. The lower court has rightly assumed that the state and condition of the patient on the 23<sup>rd</sup> February 1981 were that of a 'casualty' as defined by § 323c of the Criminal Code ... this can also be caused by the progression of an illness, provided that it takes a sudden and rapidly deteriorating turn ... this was the case, because the pregnancy had gone into the critical phase, now caused severe discomfort and necessitated immediate surgery at a clinic. This - real and crucial - assistance could not be provided*

*by the accused, he could however prepare and facilitate their implementation through his own actions. This is sufficient for the application of § 323c of the Criminal Code, because the type and level of assistance depend not only on the nature of the disaster, but also upon the abilities and potential of those obliged to assist".*

Interestingly, a progressive disease left untreated and leading to irreversible damage and even death, at a certain point can lead to the application of § 323c. In the ectopic pregnancy, it was this point at which it was discovered, because the pregnancy had entered a critical phase and caused new problems.

This point, at which a previously latent child dementia enters a new phase and is indicated by sudden symptoms, also exists in rare diseases such as Hannah's child dementia.

*"Suddenly I got sick", says a narrator in the video about Jakub ("Cuba") Schweres-Kuchta, a Polish boy, who also needs BioMarin's Cerliponase Alfa. "But then it was still quite normal. 18 months later the doctors found it: Batten disease. Since then everything has been changing presently. My legs and arms won't listen to me. I can't speak anything properly." (sic).*

<https://www.youtube.com/watch?v=6l1F08kOOn8>

The initial discovery or later acute exacerbation necessitates, as stipulated by the German Supreme Court, immediate treatment with an effective therapy in order to avoid irreversible damage.

In this situation, according to the German Supreme Court ruling, and when German law applies, everyone is obliged to help as per their "skills and abilities". A person or organisation having a substance with the properties ascribed by BioMarin's announcements to Cerliponase Alfa, is according to the ruling, once aware of the situation, while not actually obliged to provide the actual and decisive treatment, bound to its promotion and preparation within the limits of its abilities, either via a precautionary Compassionate Use program - in those countries where such an authorization is being sought and is likely - or at least its provision for an individual therapeutic trial.

Legal action by Hannah against BioMarin should therefore in Germany have a chance of success. The applicability of German law follows the internationally recognized crime scene principle (see § 3 of the Criminal Code) in conjunction with a landmark judgement of the Cologne Higher Regional Court in a matter relating to maintenance : *"The scene of a (concrete) endangerment offence is the place where the de facto offence occurred or may occur"*(OLG Cologne pp. 284/67).

[https://www.jurion.de/Urteile/OLG-Koeln/1967-10-10/Ss-284\\_67](https://www.jurion.de/Urteile/OLG-Koeln/1967-10-10/Ss-284_67)

### Individual law enforcement versus protection duty of the state

In the case decided in Cologne, it related to endangerment to a child living in Germany from unpaid alimony contributions by a foreign parent.

Due to the expected duration of such procedures, Hannah may possibly not survive without permanent damage. In this case, it should be examined whether the State could be held liable for failure in its duty to protect.

The so-called Nicholas judgement of the Federal Constitutional Court of 6<sup>th</sup> December 2005 contains one argument for this view, in which it concerns *"the duty of the state to protect life in Art. 2 para. 2 sentence 1 GG"*, *"in the extreme situation of a disease-related danger to life"*, in which the Federal Constitutional Court comes to the conclusion that *"in cases of life-threatening or regularly deadly disease, under the conditions specified above, the obligation of care-provision belongs to the core area and minimum care-provision required as per Art. 2 para. 2 sentence 1 GG"*.

[https://www.bundesverfassungsgericht.de/SharedDocs/Entscheidungen/DE/2005/12/rs20051206\\_1bvr034798.html](https://www.bundesverfassungsgericht.de/SharedDocs/Entscheidungen/DE/2005/12/rs20051206_1bvr034798.html)

Though there it related "only" to the liability of the statutory health insurance scheme for *"drugs that by the directives issued pursuant to § 92 para. 1 sentence 2 no. 6 SGB V are excluded from supply"* when however *"there are serious indications of a not so distant success of the cure, or even a significant positive effect on disease progression in any particular case"*.

But, following the same logic, from the fundamental right to physical integrity, from which the judges derive their decision, there should be a defensive right of the citizen and vice versa a duty of the state to protect, if it – as it does with compulsory insurance – intervenes in personal autonomy in health care via the restrictions of the Medical Products Act (AMG).

In fact, literature and commentary to § 21 Para. 2 No. 6, criticise that the state ineffectively pretends in its duty to protect through the facilitation of Compassionate Use and in fact illicitly undermines it.

In his publication "Barriers to Compassionate Use by the 15<sup>th</sup> Medical Products Act (AMG) Amendment" (Pharmaceutical Law 2009, pp. 323-327), the medical law expert Dr. Christian Jäkel criticized that the word "free" inserted under the framework of this amendment would act somewhat as though the legislature had added "not at all".

[http://www.jaekel-law.de/visioncontent/mediendatenbank/jaekel\\_pharmr\\_2009\\_323.pdf](http://www.jaekel-law.de/visioncontent/mediendatenbank/jaekel_pharmr_2009_323.pdf)

Jäkel considers this change of provision, - considering the stated purpose of the printed matter - is disproportionate and therefore unlawful. *"The requirement of free distribution will likely not withstand a legal review"*.

It is unlawful for two main reasons: on the one hand, because through the German insertion, the otherwise almost literally adopted and binding European legal requirement would be effectively undermined. On the other hand, because the state thus effectively excludes patients from receiving life-saving medicines. *"With the measures provided for in the 15th AMG amendment for free dispensation of Compassionate Use drugs, the legislature again deprives patients of much needed drug therapies"* (Ibid. 327).

In the extreme case a CEO or managing director, who voluntarily acted humanely at the expense of the company, could be prosecuted for embezzlement and/or recourse could be taken against him. In fact the accusation of breach of trust for such an individual therapy within Germany would, based upon § 34's presupposed statutory or extra-statutory emergency, be thrown out, depending on the legal system at the company's headquarters. Whether that also applies under foreign law for a foreign group, is an open question, as regards compassionate use domestically, when the launching and application for such a program neither makes economic sense, nor is required by law (as opposed to emergency assistance).

A colleague of Jäkel, Dr. Christian B. Fulda, was somewhat milder in his judgement, the legislature was *"obviously more inclined politically ... to prevent compassionate use"* (The Compassionate Use Regulation - more questions than answers Pharmr 2010, 517).

<https://beck-online.beck.de/?vpath=bibdata/zeits/PHARMR/2010/cont/PHARMR.2010.517.1.htm>  
(requires login)

Like prophets therefore, have Jaeckel and Fulda predicted the later development, that it should in Germany rarely come to Compassionate Use Programs - unlike in other European countries, where the word "free" was not added.

In France, where there has, since 1994, by national law been Compassionate Use as "premarket approval" (called "Autorisation Temporaire d'Utilisation de cohorte"), the pharmaceutical industry had already by 2007 used it with more than 200 products, according to the Agence française de sécurité sanitaire des produits de santé (AFSSAPS), in Germany there had been just 14 by the end of 2015 (see above).

<http://www.jonesday.com/compassionate-use-in-europe-a-patchy-frame-work-for-early-market-entry-08-20-2010/>

Normally, French children with NCL2 would be among the first to get Cerliponase Alfa from BioMarin.

*"In countries where so-called 'pre-approval access' programs are available, BioMarin will very carefully consider all the possibilities and limits for an earlier market access available after regulatory submission to health authorities."* (From the Media Statement on 5th May and 19<sup>th</sup> September, 2015, through the BR Download page)

<http://www.br.de/fernsehen/das-erste/sendungen/report-muenchen/videos-und-manuskripte/pharmafirma-verweigert-lebensrettende-medizin-100.html>

In Germany, where instead of a pre-approval access with earlier market access only a free provision under Compassionate Use would be possible, children like Hannah would not get the drug until months later with the final approval.

So it was with Vimizin (Elosulfase Alfa), currently the only drug for treating Morquio A syndrome. German patients received the drug after European approval, which took place in April 2014.

<http://www.biomin.com/products/vimizim/>

French patients have already been receiving the medication since November 2013 under the typical French variation of Compassionate Use.

*"In November 2013, BioMarin announced that Elosulfase Alfa had been granted Autorisation Temporaire d'Utilisation de cohorte (Temporary Authorisation for Use) by the French National Agency for Medicines and Health Products Safety"*.

<http://webcache.googleusercontent.com/search?q=cache:X7jA6CGKLR0J:adisinsight.springer.com/>

[drugs/800028493+&cd=3&hl=de&ct=clnk&gl=de](https://books.google.de/books?id=MHAoBAAQBAJ&printsec=frontcover&hl=de#v=onepage&q&f=false)

This intra-European difference of 5-6 months, which can decide over life and death, is a fact which speaks for itself.

The commentaries on the Medical Products Act (AMG) thus join, with good cause, the criticism of the German regulation. The comment by Erwin Deutsch and Hans-Dieter Lippert cites agreement with Jaeckel, in footnote 33 to § 21, and the one by J. Wilfried Kügel, Rolf-Georg Müller and Hans-Peter Hofmann, in footnote 83, labels the official explanation for the federal government as "an excuse".

Moreover Winnands sees, in Deutsch/Lippert in footnote 34, a collision with the "Nikolaus judgement" of the Federal Constitutional Court.

*"But if the insurance companies' costs of these treatments and medicines must be assumed, due to Art. 2 of the constitution (sic!), they should likewise not have to be issued for free by the company which is developing such drugs".*

<https://books.google.de/books?id=MHAoBAAQBAJ&printsec=frontcover&hl=de#v=onepage&q&f=false>

However, none of these authors is dealing with the fact that the insertion is only maintaining the hitherto practised German legislation where, for example, Compassionate Use with medicines against AIDS as part of "spurious" studies was possible, negotiated on humanitarian grounds between the victims associations and the pharmaceutical industry. A control group initially received a lower dose of the drug than the other study participants. *"Should ... it transpire that one of the two dose levels has greater success and/or better tolerance, this form of trial will be discontinued on ethical grounds and all participants given the same dose. To date, most AIDS drug studies had to be discontinued for these reasons".*

(Bernd Vielhaber, deficiencies in the medical care of people living with HIV / AIDS in the Federal Republic, in: Act Up:.. "A kick in the butt. The AIDS Action Group in Germany and the USA. A documentary published by Andreas Salmen on behalf of German AIDS-Support, Berlin 1991, page 117)

[www.aidshilfe.de%2Fdownload\\_file%2F8353&usg=AFQjCNEP7G0mx7jv0Q1KCBZUJ0tpjmqM6A&sig2=xqNL43gG3QM6IMDLNuhbDA](http://www.aidshilfe.de%2Fdownload_file%2F8353&usg=AFQjCNEP7G0mx7jv0Q1KCBZUJ0tpjmqM6A&sig2=xqNL43gG3QM6IMDLNuhbDA)

An ingenious evasion trick with, however, the disadvantage that there was always a commitment to free distribution and therefore the pharmaceutical industry lagged purely quantitatively behind their capacities and demand.

*"The company saw no reason to open the trial upwards. Outside of studies, there is in Europe no way for people with ARC/AIDS to get ddl. The company justified this procedure through the lack of availability of the drug, which is not produced on an industrial scale.*

*I consider this argument to be an excuse. Rather, economic considerations are pivotal for limiting the number of participants. It is considerably more expensive to produce medicine, so to speak 'by hand', than in large-scale production. In addition, Bristol-Myers must provide ddl, as long as it is*

*not yet approved, free of charge. Only after the (provisional) approval by the BGA, can the drug be marketed"*(Vielhaber, *ibid.*, page 118).

If the state, as part of its duty to protect, not only wanted to lead such circumvention back on track, but also to remedy the lack of a life-saving drug for those affected, it would not have copied the free provision out of the old de facto regime into the new one. What it does in practice, was already sufficiently tested, analysed, criticized and documented in order to make the pre-programmed failure of Compassionate Use predictable, with the insertion of the word "free".

Conversely, it is not apparent that the suspected evasion of studies through Compassionate Use in a careful weighing up of interests would actually be evaluated as the greater damage in comparison to the present situation. If the data obtained through Compassionate Use did not suffice to allow a drug to be approved, the EMA as regulatory authority would be obliged not to do it, but to require further studies. Consequently the only damage would be the spending of public money to save lives in the framework of the AHMV regulations. But when it comes to money versus human lives, in a law-compliant consideration of the legal interests, the decision can only be in favour of life.

Even if a substitute is a legal obligation under the applicable law, at least for enabling individual therapy trials based on § 323 of the Criminal Code, it is not sufficient for the purposes of this duty of protection, if the state leaves it to case-by-case litigation between two unequal opponents, the needy patients and the pharmaceutical companies, because it could be anticipated that even in summary proceedings the courts would in the end only have to decide on the allocation of the costs of the parties, *"after a mutual interim injunction... resolved itself due to the death of the plaintiff"*. (Quote from a decision by the OLG Frankfurt 16 from 5<sup>th</sup> March 2015 in the transplantation case Dönmez ./ UKGM, 16 U 192/14).

<https://openjur.de/u/767410.html>

To prevent such outcomes, ethics committees should, within the meaning of § 3 para 2c GCP-V, consider themselves obliged, under law, while evaluating pharmaceutical companies' plans for studies, to improve *"the protection of the rights, safety and well-being of the affected persons"* to the benefit of persons who are affected by the study, as participant or potential participant or non-participant patients, also thereby that they make a condition upon the company of a clear commitment to Compassionate Use and/or the release of the drug to individual therapy trials during the clinical trial or otherwise to withhold their consent to the trial, because they are not convinced of the *"consideration of foreseeable risks and disadvantages of the clinical trial against the anticipated benefits for the persons affected and future ill persons"* (for example, Hannah or Miguel) according to § 7 para. 3 no. 2 GCP-V without such a commitment and because *"the public trust"* in the ethics of pharmaceutical research is not a given, which not least is proven by the over 400,000 signatures on #savehannah.

<https://www.gesetze-im-internet.de/gcp-v/BJNR208100004.html>

Alternatively the inserted word "free" could also be deleted again, through which individual therapy trials, as necessary, would still necessitate free emergency assistance, however Compassionate Use programs would offer the pharmaceutical industry a possibility of evasion.

To compensate would be to ask what the legislature would have to do to simultaneously help avoid

any unacceptable delay or obstruction to drug approval as an unwanted side effect resulting from individual therapy trials or Compassionate Use, which pharmaceutical companies and patients' representatives apparently fear. For this purpose, these fears need to be substantiated in the shape of the underlying scenarios.

Unfortunately in the above quotes, no precedents were named in which the legal administration of an as yet unapproved medication in an individual therapeutic trial or in the framework of Compassionate Use delayed or thwarted the subsequent approval of a drug. According to the federal authority responsible for Compassionate Use, there has never been such a case: *"However, the BfArM is aware of no known case wherein authorization was not granted solely because of an adverse reaction report from a drug hardship program"* (From an email of the Federal Institute for Drugs and Medical Products on 27<sup>th</sup> October 2015 to the Bavarian radio service, made available to the Relief Centre cf. the ARD report from 1<sup>st</sup> January 2015 in "Report München").

<http://www.br.de/fernsehen/das-erste/sendungen/report-muenchen/videos-und-manuskripte/pharmafirma-verweigert-lebensrettende-medizin-100.html>

A - purely hypothetical – but conceivable risk for the pharmaceutical industry could arise in the disclosure requirement pursuant to § 6 i.V.m. § 8 paragraph 3 AMHV, through which the supreme federal authority shall be informed of any suspected case of serious side effects which occurred as part of a Compassionate Use program, and which they in turn must report on to the European Medicines Agency. Hence the approval might actually be slowed or become impossible. Of course that would only be harmful if the regulatory authority were to erroneously judge in such cases, or through uncertainty call for unnecessary further studies. Such a case is, as mentioned, at least to the BfArM unknown.

It would indeed be fatal if the EMA, as a regulatory authority, negatively rewarded a Compassionate Use Program by switching from the "150 +" day limit to the "210+" day limit on the grounds that special haste were no longer in the public interest, because patients now get the drug without approval.

It is impossible however within an individual therapy attempt, as applied for by Miguel and Hannah, for the disclosure requirement pursuant to § 6 AMHV, to lead to delays in the approval, since it is not applicable (§ 1 AMHV).

## Special case: The refusal during ongoing studies with placebo

In the discussions between pharmaceutical companies and patient representatives an entirely different argument has been encountered, which even gainsays isolated individual therapy trials during ongoing studies, at least when they are so-called controlled studies, and especially on children.

Biogen is now running the SMNRx-studies for ISIS (now "IONIS") Pharmaceuticals in Germany. Biogen explained the refusal to provide the drug for individual therapeutic trials to a patient spokesperson approximately as follows:

*"This study has a placebo group, that is, 1/3 of the children in the study received only a placebo. Now in Compassionate Use Miguel would definitely receive the drug. Parents who have embarked on the study and afterwards find that the child received a placebo for 2 years could perceive that as unjust"*(Quote from the report to the Relief Centre by a patient representative, paraphrasing his conversation with Biogen).

The logic of this argument is immediately comprehensible, but raises ethical and legal questions to the study itself (Tender document questions 2 to 7).

The pharmaceutical industry is here stuck in an almost classic dilemma: the very studies in which Compassionate Use and individual therapy trials would be permitted, are also the only ones where, according to the Declaration of Helsinki (DoH), placebo groups are still permitted. As soon as there is a proven effective treatment, this must be performed in the control group and the new preparation compared to it.

[http://www.bundesaerztekammer.de/fileadmin/user\\_upload/downloads/DeklHelsinki2013.pdf](http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/DeklHelsinki2013.pdf)

As Biogen's argument shows, there can only be one or the other: either one makes a placebo group, and then no Compassionate Use program or provision of the drug for individual therapy trials. Or there is Compassionate Use and/or the new drugs are made available for individual therapy trials, but then there may be no placebo group.

The latter could, however, jeopardize the approval of the drug because the scientific evidence of its efficacy and safety has not been provided within the framework of the existing possibilities.

However, the regulatory authority has, in certain cases, shown understanding. The control group can be dispensed with, given good cause. This is the case in the studies with Cerliponase Alfa, the drug that could help Hannah. The important reason is that otherwise, to simulate the administration even in the placebo group, an operation would have to be carried out on the skull. That could be disproportionate because of the risks and would therefore have to be rejected by the ethics committees.

*"'Sham surgery' is only justifiable if that patient group is not exposed to the risk of serious or irreversible damage through the operation. In the event of doubt the ethics committees have the task of clarifying what can be considered in the study as 'slight disorders' or 'minimal risk'. In addition these establishments have to weigh up in individual cases whether the additional risk of placebo administration is justified"*(Opinion of the Scientific Advisory Board of the German Medical Association, read and endorsed by the Executive Board 25<sup>th</sup> March 2010).

<https://www.aerzteblatt.de/archiv/77606>

Any gain in knowledge is contradicted by several decades of research in Hamburg on NCL2 children under the direction of Prof. Kohlschütter, where, in studies, the untreated progression was well documented.

(Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. Steinfeld R, Heim P, von Gregory H, Meyer K, Ullrich K, Goebel HH, Kohlschütter A. Am J Med Genet 2002 Nov. 1;112(4):347-54).

<http://www.ncbi.nlm.nih.gov/pubmed/12376936>

However, according to Dr. Inge Schwersenz, the patient's spokeswoman for SMA at the European Medicines Agency (EMA), the case with Miguel's illness is identical: *"Even with SMA I one could do without a placebo group, as data on the so-called Natural History, as with NCL2, are most robust and can be used as a historical control"* (Email from 22<sup>nd</sup> December 2015 to the Relief Centre).

The most recent release of such data for the Natural History of SMA was from observational studies in preparation for subsequent drug studies in 2009 and 2014.

(Observational study of spinal muscular atrophy type I and implications for clinical trials. Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, Kang PB, Foley AR, Yang ML, Martens WB, Oskoui M, Glanzman AM, Flickinger J, Montes J, Dunaway S, O'Hagen J, Quigley J, Riley S, Benton M, Ryan PA, Montgomery M, Marra J, Gooch C, De Vivo DC. Neurology. 2014 Aug 26;83(9):810-7. doi:10.1212/WNL.0000000000000741. Epub 2014 July 30).

<http://www.ncbi.nlm.nih.gov/pubmed/25080519>

(Genotype-phenotype studies in infantile spinal muscular atrophy (SMA) type I in Germany. implications for clinical trials and genetic counselling. Rudnik-Schöneborn S, Berg C, Zerres K, Betzler C, Grimm T, Eggermann T, Eggermann K, Wirth R, Wirth B, Heller R. Clin Genet 2009 Aug;76(2):168-78. doi:10.1111/j.1399-0004.2009.01200.x).

<http://www.ncbi.nlm.nih.gov/pubmed/19780763>

However, it must be remembered that researchers are sometimes of the opinion that data from such preparatory trials for drug studies are not sufficient to prove the efficacy of a drug, even in SMA Type I. Because even if there is no standard drug, at least a non-drug "Standard of Care" exists. This is also the case with SMA, where it is unknown even to some paediatricians and even some child neurologists, however, so that the optimal care and of the advisory support of parents in the three German specialist clinics can itself leave the study participants in the placebo group looking better than those in the Natural History trials, without this positive difference being attributable to the drug being tested.

But even if this argument can not be dismissed out of hand, the logical consequence to overcome this difference is not a placebo group, but the elimination of ignorance in child neurologists and paediatricians in general and in particular in the doctors participating in preliminary trials to Natural History patients. Their study leadership must ensure that here too, the same up-to-date

standards of care are adhered to, then this difference disappears and there is no longer an argument for a placebo group.

This solution would have to be self-evident for ethical, professional, and possibly also legal reasons. Paediatricians who diagnose such diseases wrongly or not at all and/or do not refer them to a paediatric neurologist, and specialists who do not know the current standard of care and do not advise and/or treat accordingly, could thereby enter into a liability risk.

However, even if the existing data is not sufficient rigorous scientific proof as this was not followed during its collection, in cases where the probability of death for participants in a placebo group is approximately 100 percent, a comparative question needs to be asked: is having to die not as equally disproportionate as the mere risk through surgery in order to feign the administration? Or is an unnecessary surgical risk or the risk of a lumbar puncture more serious than certain death?

This cannot be, for the simple reason that in the justification process for lifesaving interventions for patients incapable of giving consent, the opposite is assumed: in comparison to omission of treatment, taking those risks is from a legal perspective the lesser evil, if a serious diagnosis or a serious suspicion exists.

As long as there is no convincing rebuttal of this argument, it must be doubted whether the ethics committees repeatedly sanctioned practice is legal, of refraining from placebo groups in trials for drugs without standard when the pretence involves surgery risks, excepting when the non-treatment during the study period means a high probability of an inevitable fatal outcome.

There needs to be even more doubt about the legality of Biogen and ISIS Pharmaceuticals (or rather IONIS)' selected loophole, in Miguel's case, on top of placebo recipients also to refuse every help to people outside the study, in order to be able to work with placebos within the study. When the one prevents the other, do we, through the requirement of a placebo group, win a (not impossible in the case of risks) justification against the de facto failure to render assistance within and without the study, or does this relationship reverse itself, so that the administration of placebos becomes legally impossible due to the, presumably positive, duty of assistance in the face of threat of death or permanent damage.

The same question applies to the decisions of the ethics committees, who each time weigh the gain in knowledge against the risks from administration of a placebo, and have to take the, for some, potentially lethal consequences into account.

The committees could, in their considerations, actually orientate themselves on the above cited stipulation of the German Medical Association, adopted in the recommendations for ethics committees. They interpret the DoH more severely than it intends, by generically and without restriction formulating "*also the patients who receive placebo will not be subject to any risk of serious or irreversible harm*".

[http://www.medizin.hhu.de/fileadmin/redaktion/Fakultaeten/Medizinische\\_Fakultaet/Dekanat/Dok\\_Ethikkommission/Mitglieder\\_der\\_EK/Empfehlungen\\_zur\\_Begutachtung\\_klinischer\\_Studien\\_durch\\_EK\\_2012.pdf](http://www.medizin.hhu.de/fileadmin/redaktion/Fakultaeten/Medizinische_Fakultaet/Dekanat/Dok_Ethikkommission/Mitglieder_der_EK/Empfehlungen_zur_Begutachtung_klinischer_Studien_durch_EK_2012.pdf)

Even more, the supposedly indispensable existence of the placebo group offers no justification for a de facto homicide (to persons within the test) or failure to render assistance (to persons without

the test), if the placebo group - in the context of balancing these consequences - would have been unnecessary. That would be the case if from a scientific perspective enough data had been produced from preparatory studies in wise foresight, before any pharmaceutical company was ready to test a new drug in phase 3. What level of certainty can be achieved here would have to be discussed in medical discourse and above all comparatively evaluated through metastudies. If this type of research could light a way out of the ethical and legal dilemma, it would be worth the trouble, especially since it is likely to be neutral in terms of effort: That which will be invested in preparatory studies for Natural History, can be saved later in the drug trials themselves. In both studies, the best possible would be done for the patients without someone having to be sacrificed, who could have been saved.

In practice, such research could however again presuppose a legal interest consideration because the central database for rare diseases at orpha.net would have to be transferred into a register, which seems justified, given the officially declared "priority" of the research of such diseases, even by the cost-benefit ratio. To be able to develop a probable effective drug is, due to the methodology of genetic research since the turn of the millennium, no longer the big problem: through gene analysis the location of the defect is established, from which it may be deduced which enzymes could compensate. In biological compounds side effects are fairly unlikely. The problem is the data proving their effectiveness. A mandatory register could help, with little effort, to improve the data situation considerably.

In study practice it is not ultimately the pharmaceutical companies who decide, but the biostatistics experts from the regulatory agencies, how many study participants should be recruited for an acceptable proof - even if and when enough "hard" natural historical data were available – from a scientific point of view, if not a legal one – in order to be able to omit further natural history surveys into a rare disease, such as a placebo arm. Contrary to what the Federal Health Minister said, the decision on Compassionate Use is, according to German AMHV, therefore not "solely with the pharmaceutical companies," but in these cases factually with the EMA in England or the FDA in the US. But that also does not protect their employees, in strictly legal terms, of punishment if they make a mistake in their assessment of this question, when for others it is a matter of life and death.

Whether this, in turn, protects the pharmaceutical companies, is another question. Ultimately, they would have the alternative, to close the placebo arm with the risk that in fact in this case admission would be delayed, without this meaning a disadvantage for any patient, because Compassionate Use would indeed be started earlier for all - provided the BfArM evaluated the safety and efficacy data submitted as being positive.

If the rights issue is also answered in the affirmative, that therapeutic trials and/or Compassionate Use are always then legally bidden, when they are permitted by law, then for trials in Germany with a placebo-arm for severe and life-threatening illnesses there would be the consequence that the placebo control would be cancelled and all participants of the study would be treated with the new drug, *"as soon as its effectiveness is so established such that the disadvantages of the placebo treatment are medically no longer justifiable"* (Statement by Biogen to the Relief Centre on 5<sup>th</sup> February 2016).

Indeed, there are pharmaceutical companies, which follow § 40 para. 1 sentence 3 no. 2 AMG word for word. As a result of this provision, clinical testing of drugs on human subjects should only be performed if and so long as *"the foreseeable risks and drawbacks compared to the benefit to the*

*person upon whom it is to be carried out (person affected), and the likely importance of the drug for the medicine are medically justifiable".*

The question is: who decides, and by whom and on what basis will checks be made, when the *"effectiveness is so established such that the disadvantages of the placebo treatment are medically no longer justifiable"*? The pharmaceutical company? The EMA as a European monitoring body? A national institute like BfArm? Or the regional ethics commission, which endorsed the placebo designs? Is this point reached when the national criteria for Compassionate Use are met? Or must the European criteria be met for admission?

If there is general agreement that the "handling of test substances at an early stage ... does not lie in the private autonomy of companies and patients and their families" but must be "according to the guidelines of our legal order only under the terms imposed by the legislator", these issues should not be decided under private autonomy.

The current situation is unsatisfactory because Biogen reaches negative verdicts from a business perspective on this question ( "Such a knowledge situation does not exist within our company"), while more than 100,000 signatories of the Fast-Movement-Petition answer it positively on the basis of success stories from IONIS ( formerly ISIS).

<https://www.change.org/p/help-spinal-muscular-atrophy-sma-patients-get-the-life-saving-treatment-they-need-approved>

What speaks against having it objectively checked, in that IONIS, as the petitioners are calling for, through presentation of the data in the United States, makes an application to the FDA for "Accelerated Approval" or that Biogen independently clarifies the question in Germany by applying for Compassionate Use with BfArm?

Could this be an obligation, ethical or even legal, if lives depend on it, and there are good grounds for believing that this could be approved?

Sometimes it is feared that just the opposite will be achieved by such questions because pharmaceutical companies evade them through future studies in the Third World, to be able to use the lower ethical and legal standards there, as soon as we ask such questions here or improve standards at the expense of the companies. From the perspective of the Relief Centre that can not be a case against improvements or even against the clarification and enforcement of applicable law. As long as companies want to be on the American or European market, Europe and America have to decide which ethical standards of "Good Clinical Practice" (GCP) must be proven by external studies. The EMA is already thus preventing an ethical dumping competition.

*"EMA and national authorities work closely with international partners to ensure that studies underpinning marketing authorisations in the EU are carried out to the highest standards and that the companies involved comply fully with all aspects of Good Clinical Practice (GCP)".*

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/GVK\\_Biosciences/human\\_referral\\_000382.jsp&mid=WC0b01ac05805c516f](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/GVK_Biosciences/human_referral_000382.jsp&mid=WC0b01ac05805c516f)

## **Ineffective consent with coercion or incomplete education of adults**

Secondly, independently, the "informed consent" of subjects provides no justification for a de facto

homicide, nor even for the interventions during the study per se, if this consent is fraught with so-called "vice of consent", whether by concealment of legally available alternatives of gaining access to the drug, or whether by a consistent refusal of due assistance through Compassionate Use or individual therapy trials with the aim of forcing such assistance seekers to participate in studies.

*"The consent must not suffer from significant deficiencies ... In any case, consent based on coercion, obtained by deception or through any other breach of medical duty to inform, is always void"*(Wessels/Beulke, StrafR AT § 9 para. 376).

<https://books.google.de/books?id=yEiXAJvBNTUC&printsec=frontcover&hl=de>

For this reason, under federal law, the templates used by the sponsors for prospective participants in studies inform, in item 6, on alternatives: *"For the treatment of your condition the following possibilities are also available ..."* (federal template).

<https://www.aeksh.de/dokument/vorlage/klinische-pruefung-eines-arzneimittels-mit-volljaehrigen-einwilligungsfaehigen-patienten>

<ethikkommission.blaek.de/docs/unterlagen-amg/klinische-pr%C3%BCfung-eines-arzneimittels-mit-vollj%C3%A4hrigen-einwilligungsf%C3%A4higen-patienten.doc?sfvrsn=0>

If a new drug was made available, not just within the study but also for Compassionate Use and/or individual therapy trial, it would be necessary at this point to inform of the same, actually over the legal possibility of an individual healing attempt. The question is whether the interested parties would still agree to participate in a controlled study with placebo risk.

It may be assumed that in this case placebo studies would not become completely impossible, but certainly much more expensive. Business disadvantages, however, are in accordance with § 323c StGB considered acceptable as a result of rendering assistance, especially as the pharmaceutical industry generally recoups its development costs via the price, even more so in new drugs with "orphan drug" status, which, inter alia, benefit from extended patent protection.

But, in a placebo study, this freedom of choice would no longer be burdened with lack of consent so that here – at least in adults able to consent - there may be justification, even if de facto an assault or homicide had taken place.

That these may diagnostically be the facts of the case, at least, appears to be undisputed. Andrea Loose, in 2003, summarised the legal situation unequivocally as part of her dissertation:

*"The assignment of the affected person concerned to a placebo group and the associated non-treatment with an established method can lead to affirmation of a de facto criminal act in the sense of assault or homicide"*(A. Loose, Criminal limits of medical treatment, page 194).

[http://www.jurawelt.com/sunrise/media/mediafiles/13797/tenea\\_juraweltbd47.pdf](http://www.jurawelt.com/sunrise/media/mediafiles/13797/tenea_juraweltbd47.pdf)

Since in the meantime Compassionate Use and individual therapy trials are based on an improved legal foundation, the question would today be whether this principle also applies to non-treatment of the control group through Compassionate Use or individual therapy trials, and not only to non-treatment with "established" or (as the DoH instead calls it) "proven" methods. The "Nicholas

judgement" of the Federal Constitutional Court clearly implies that the difference, for orthodox medicine huge, is juristically no difference.

## **The legally questionable group benefits for minors**

For minors, the legal situation is again different. Since they are not yet capable of giving consent, justifications for de facto assault or homicide can not be derived from their "informed consent". Neither they nor their parents can effectively consent to an injury if it becomes apparent that the injurious intervention was not in the interest of the child.

In the past the solution was to weigh the benefits for them, from the outside. Humane experiments, for instance on sick children, were in the past therefore only allowed if they were simultaneously attempts at treatment.

However, before the amendment, the pharmaceutical industry tried to go a step further through the construction of a so-called "group benefit". Human trials on minors should even then be legitimate when they have no disease-related personal benefit to the individual child or young person, but for others who are suffering from the same disease.

This was already rejected in 2003 in the context of legal research. *"Since an overriding interest for the affected person is lacking in measures for the benefit of others, these do not correspond with the best interests of the person concerned. This applies even if the proposed measure is only associated with minor negative effects and risks or it is a measure with purely group benefit"*(Andrea Loose in her above-cited thesis, page 196f).

Nevertheless, the intention of the legislature in 2005 as part of the 14th AMG amendment was that a group benefit should suffice to legitimize human experiments on them, by stating that *"The clinical investigations must be connected with a direct benefit for the group of patients suffering from the same disease as the person concerned"*(§ 41 paragraph 2 no. 2 letter a AFG N.F.).

Doubts about its constitutionality were loud, but these remain to date unexplained. For example the medical lawyer Dr. Michael Pap from Karlsruhe, expressed criticism in a lecture on 23<sup>rd</sup> February 2005 in front of the National Ethics Council:

*"The amendment of § 41 para. 2 no. 2 AMG encounters constitutional objections with respect to group beneficial drug testing of minors not having the ability to consent should the physical integrity of subjects be injured or their health exposed to hazards"* (Dr. Michael Pap, lecture on 23<sup>rd</sup> February 2005).

<http://www.ethikrat.org/dateien/pdf/wortprotokoll-2005-02-23.pdf>

Should these constitutional objections to the group benefits be justified, this exacerbates the adult dilemma described above. The lack of an individual benefit for minors can be fixed neither by enlightened consent nor through such group benefit, such as to legitimise the injurious procedures within the framework of any human experiment or worse.

At most an "unavoidable mistake of law" in accordance with § 17 Clause 1 of the Criminal Code could grow out of an unconstitutional provision, giving doctors and pharmaceutical companies impunity, without cancelling the consequential duty of omission. The lack of clarity in constitutional concerns is therefore not in the interests of the pharmaceutical industry, nor the

public, and certainly not in the interests of sick minors.

Even the argument that a person taking part in a controlled study with a placebo group would at least be better off than a non-participant, solely on the grounds that they would at least have the chance to get the real product, no longer convinces, if there are Compassionate Use and individual therapy trials offering the real drug outside of the study. Any Compassionate Use or individual therapy program would, with underage participants, immediately make the study illegal. The question remains even with minors, whether this dilemma can be circumvented by consistently refusing both in order to protect the legality of the studies, although legally permissible, and perhaps even necessary as an emergency aid.

## Can a legal situation resulting in death have legal consequences for politicians?

Given this state of affairs and a potentially self-contradictory legal situation there remains the question of whether action is needed by the legislature as part of its duty to protect, but also whether responsible politicians can be made not only politically but also legally responsible.

The German justice system has only twice, in post war times, been confronted with the question of whether politicians can be held accountable for legislation leading to death: once in the years 1991 to 2004 in the case against members of the former East German Politburo. And then in early 2004 a charge against Health Minister Ulla Schmidt, presented by Hameln lawyer Rüdiger Zemlin to the Hanover public prosecutor on behalf of the taxi driver Bernd Wente for the destitute dialysis patient Günther Walter M. deceased on 13<sup>th</sup> January 2004 (cf. the final sentence of the Reuters report).

<http://www.spiegel.de/politik/deutschland/tod-eines-dialysepatienten-anzeige-gegen-gesundheitsministerin-schmidt-a-282592.html>

In a presentation published on the internet, Rüdiger Zemlin justified the accusation of negligent homicide against the Minister of Health and others as follows:

*"The legislative process was carelessly done - with the result that the possibility of death and serious physical consequences through non-treatment became acceptable".*

<http://archiv.randzone-online.de/fp/fp040120.htm>

That finding would result - if it is true - at best in the offence of endangerment. It would only become homicide if it were to cause someone's death. That, however, was ruled out by the prosecutor's office in the case of Günther Walter M., reported at the time by the Deister-Weser Zeitung:

*"According to the preliminary autopsy result there is no connection between the death of the man and the missed dialysis" said senior public prosecutor Klinge. Coroner Joachim Eidam had examined the corpse. Günther Walter M. had died of central cardiovascular failure, said Klinge. "M. had a serious heart condition, had a pulmonary oedema; Small intestine and duodenum were inflamed", said the senior public prosecutor. "There was no evidence of medical malpractice".*

<http://www.sdc-forum.de/84944-post3.html>

<http://archiv.randzone-online.de/rand/rand040124.htm>

Physicians doubted that the conclusions drawn by the public prosecutor from the autopsy results were technically correct. Dr. Wolfgang Michling told the Red Flag: *"The shift of dialysis by just one day may cause pulmonary oedema, atrial fibrillation, cardiovascular failure and death".* - Exactly what the autopsy had found.

<http://rotefahne.mlpd.de/rf0404/rfart10.htm>

But a proceeding to force criminal prosecution after §§ 172 ff. Code of Criminal Procedure would have required an injured party, and no one dared to up the ante toward obstruction of justice. Therefore, at the time the interesting legal question remained unanswered, whether West German politicians and ministry officials could be prosecuted for poor decisions resulting in death due to guarantor status, in the same way as members of the Politburo after the Wall fell.

In certain departments, upon whose politics lives may depend, for example Defence, Home affairs, Health or Transport, there is at least a temptation, to neglect on cost grounds the duty to protect these people. It is widely acknowledged that particularly healthy public finances, low taxes and stable health insurance contributions are decisive in elections. The electorate hears nothing of individual fates that can be its price, unless they are so spectacular that they have news value, and each could worry that the same could befall him.

The death of the lawyer Andrea Sloan in the United States caused a legal amendment that at least facilitated therapeutic trials and compassionate use there. To save the lives of Hannah and Miguel or at least to draw the right conclusions from their deaths, if they should be inevitable, it must therefore first be checked whether the current legal situation tacitly accepts the death or whether someone may here be prosecuted for dereliction.

Federal Health Minister Hermann Gröhe clearly summarised the legal opinion of his ministry in 2015 one day before Christmas Eve: *"The decision to provide a medicinal product under medicines hardship regulation lies solely with the pharmaceutical companies. They also carry the criminal and civil liability for the use of the drug. There is no legal recourse to oblige the US company to make a drug, unauthorized in Germany and the EU, available through Compassionate Use"* (From a letter from the Federal Ministry of Health/BMG on 23<sup>rd</sup> December 2015, the auxiliary body present).

That should, in several respects, be legally scrutinized: On the one hand, if it is really the case and not that criminal law already provides a handle to at least force provision of the drug for individual therapy trials where these are possible, and, on the other hand, even when impossible, whether this has to or may remain, and to uphold the legislature on the grounds of its duty to protect, to at least eliminate the barriers it has either created itself (unlike France or Spain), or which come into being through an ethically and legally dubious study process involving placebo groups and death as an indirect consequence for non-participants.

## **Final appeal**

The rights issues here compiled and explained in a lay pre-analysis require a detailed technical investigation and its subsequent debate in the context of a public legal discourse.

A discourse on medical and economic problems affecting the refinancing of pharmaceutical research for rare diseases was launched by interested parties in the last month in a frontal attack on the Orphan Drugs Regulation (EC) No. 141/2000.

*"In order to be able to offer a safe drug therapy to rare disease patients, the G-BA (federal joint committee), in justified individual cases, even with the benefit orphan drugs – needs to be able to fully examine the benefits and potential for damage. Here a change of law is urgently needed "*, claimed the GKV-Spitzenverband (association of statutory health insurance funds), representing all statutory health and nursing care insurance, on 21<sup>st</sup> January 2016 in a press statement. An analysis, carried out at the turn of the year, of all the reviews by the Federal Joint Committee (G-BA) from

2011 to mid-December 2015, resulted in the perception of the statutory health insurers in almost half of the drugs approved by the EMA for rare disorders: *"The scientific database is not sufficient to assess the extent of added benefit"*.

[https://www.gkv-spitzenverband.de/presse/pressemitteilungen\\_und\\_statements/pressemitteilung\\_339584.jsp](https://www.gkv-spitzenverband.de/presse/pressemitteilungen_und_statements/pressemitteilung_339584.jsp)

*"In its press release of 21<sup>st</sup> January on the added value of new drugs, the GKV-Spitzenverband arouses the impression that it is regularly obliged to refund medications for people with rare diseases, which would pose a risk to the patient. For people living with such a serious illness, this press release is almost cynical!"* Counters ACHSE as lawyer for the affected. *"The GKV's proposals serve, in our assessment, not to improve care of those affected, but should save costs"* (Press release of 25<sup>th</sup> January 2016).

[http://achse-online.de/cms/informationen/pressemitteilungen/pressemitteilungen.php?we\\_objectID=748](http://achse-online.de/cms/informationen/pressemitteilungen/pressemitteilungen.php?we_objectID=748)

*"These new drugs can mean progress"*, the health economist Prof. Jürgen Wasem, chairman of an arbitration body between the G-BA and the pharmaceutical industry, quoted already on January 7 by Julia Friedrichs in German Time magazine on the cost-benefit relationship of new anti-cancer drugs. *"But drugs like these present us with a fundamental question: How much is society willing to pay for the hope of longer life?"* (Julia Friedrichs, Verschreibungspflichtig/On-prescription, German Time Magazine No. 2, 7<sup>th</sup> January 2016, p. 16ff, quote from page 18).

<http://www.zeit.de/zeit-magazin/2016/02/medikamente-krebs-hexavar-markt-neuheit-risiko>

A legal policy decision of the alternative "money or your life", or rather a balancing of survival of the one against the prosperity of others, but should not be addressed alone under premises of purely biostatistical evidence and/or health economic considerations without consideration of basic law on fundamental rights issues and ethical principles.

Convincing answers to the legal questions collated here can therefore through the textually-related discussion serve legal certainty, the right of peace, law enforcement or the development and unification of the law, which - if it is done carefully – will serve the interest of all involved parties, the person seeking healing, pharmaceutical research and industry, the people in the health and helping professions, the judiciary, policy makers and ultimately the general public.



# Diagnose ohne Mitgefühl

**Medizin** Ein Niederländer baut eine Onlineplattform für noch nicht zugelassene Medikamente auf. Auch in Deutschland warten Schwerkranke auf die neuen Wirkstoffe, meist vergebens. Patienten sterben, weil die Hürden zu hoch sind.

Als der Anruf kam, war Ronald Brus in seinem Ferienhaus in Südfrankreich. Die Atlantikküste lag verlassen da. Er hatte das Gebäude einen Tag zuvor gekauft. Im Sommer, so seine Hoffnung, würde er hier mit der Großfamilie Urlaub machen.

Sein Vater war am Telefon. Er atmete schwer. Er weinte. „Ich habe Lungenkrebs“, sagte er. „Ich werde dein Haus nicht mehr sehen.“

Wenige Wochen später versuchten Ärzte, den Tumor herauszuschneiden. Die Metastasen kamen trotzdem.

Ronald Brus, selbst Doktor der Medizin, stand damals an der Spitze einer niederländischen Firma, die Impfstoffe herstellte. Seit mehr als 20 Jahren arbeitete er in der Pharmabranche, er hatte Geld und Kontakte. Ein Kollege berichtete ihm, dass in den USA gerade neuartige Medikamente gegen nicht kleinzelligen Lungenkrebs getestet würden.

Vor allem ein Präparat namens Keytruda werde als Wundermittel behandelt.

Doch der Wirkstoff war noch nicht zugelassen.

Um seinen Vater zu retten, wollte Brus das Medikament unbedingt haben, sofort. Er telefonierte mit Ärzten und Pharmafirmen. Er arbeitete sich durch Gesetzesvorschriften, stellte einen Antrag bei den niederländischen Behörden. Er ahnte, dass er zu spät sein würde.



MARKEL REDONDO / DER SPIEGEL

**Medikamentenabfüllung, Unternehmer Brus vor seinem Ferienhaus in Südfrankreich: „Ich habe eine große Idee“**

In vielen Arzneimittelstudien werden Wirkstoffe gegen Erkrankungen getestet, für die es bislang noch keine Therapie gibt. Es sind potenzielle Medikamente für Menschen, deren wichtigste Frage lautet: Wie lange habe ich noch zu leben? In zahlreichen Industrieländern gibt es gesetzliche Ausnahmeregelungen, um schon vor der Marktzulassung an solche Mittel zu gelangen. Der Fachausdruck lautet *Compassionate Use*: Gabe aus Mitgefühl.

Bisher jedoch ist dieses Mitgefühl die Ausnahme, nicht die Regel.

Brus beschloss, einen Onlinehandel für solche noch nicht zugelassenen Medikamente zu eröffnen. Er verkaufte seinen Anteil an der Pharmafirma und beantragte eine Lizenz zum Vertrieb pharmazeutischer Mittel. Er investierte 2,7 Millionen Euro, stellte Juristen ein, Apotheker, Programmierer, Ärzte.

Vor etwas mehr als einem Jahr ging seine Plattform *MyTomorrows* online: eine weltumspannende Datenbank, die experimentelle Medikamente gegen lebensbedrohliche Krankheiten enthält. Jeder Patient kann seither auf der Plattform einsehen, ob es einen Wirkstoff gibt, der ihm helfen könnte – und er erfährt auch, wie er ihn bekommen kann.

Inzwischen zählt die Onlinebörse 30 000 Suchanfragen pro Monat. Auf seinem Handy kann Brus jederzeit verfolgen, nach welchen Krankheiten am häufigsten gesucht wird. Die aktuelle Statistik:

Platz 3: Prostatakrebs

Platz 2: Hautkrebs

Platz 1: chronisches Erschöpfungssyndrom.

Mit *MyTomorrows* hat der Niederländer eine Öffentlichkeit hergestellt, die es vorher so nicht gab. Brus hat, so könnte man es sagen, die Speisekarten aller Pizzerien

dieser Welt in einer großen Liste zusammengefügt. Jetzt möchte er erreichen, dass man möglichst viele dieser Pizzen direkt bei ihm bestellen kann. Und damit beginnt das Problem.

Brus kann die neuen Medikamente nicht einfach so verschicken. Jedes *Compassionate-Use-Programm* muss von den jeweiligen nationalen Behörden genehmigt werden; denn niemand weiß genau, wie sicher die Präparate sind. Ein noch nicht zugelassenes Medikament ist eben keine Pizza.

Ronald Brus empfängt Besucher in seiner Firmenzentrale in Amsterdam, Pilotenstraat 45, ein Großraumbüro im dritten Stock. Hinter klobigen Holztischen: Erdem, Mitchell, Siebrig, alle per Du. Brus, 53 Jahre, Manschettenknöpfe, Einstecktuch, ist ein Mann, der nicht gern still sitzt. Mitten im Gespräch springt er auf, läuft zur Tafel an der Wand und malt einen lang gestreckten Pfeil. Darüber schreibt

er: „Zehn Jahre“. So lange dauere es im Schnitt, bis ein neues Medikament auf den Markt komme.

In diesen zehn Jahren muss sich das potenzielle Arzneimittel in drei klinischen Phasen bewähren, in denen es an Menschen getestet wird. Der Wirkstoff wird dabei nicht mehr verändert.

„Wir nennen diesen Zeitraum ‚Entwicklung‘, aber tatsächlich wird nichts mehr entwickelt“, sagt Brus. Wie viele schwer erkrankte Menschen, fragt er aufgebracht, müssten sterben, weil ihnen ein Medikament auch nach zwei erfolgreichen Studienphasen noch vorenthalten werde?

Mit seiner Plattform gehört er zu den Pionieren einer Bewegung, die für einen leichteren Zugang zu experimentellen Medikamenten kämpft und vor allem in den Vereinigten Staaten starken Zulauf hat. In bisher 31 amerikanischen Bundesstaaten setzten Aktivisten und Patientenorganisationen in jüngster Zeit „Right to Try“-Gesetze durch, die sterbenskranken Patienten das fundamentale Recht zusprechen, selbst zu entscheiden, ob sie ein neues Mittel bereits vor der Zulassung ausprobieren möchten. Keine staatliche Stelle darf ihnen diesen Wunsch mehr verwehren. Es ist der amerikanische Freiheitsgedanke in seiner reinsten Form.

Die Forderungen europäischer Aktivisten sind weniger radikal. Noch glauben hiesige Patientenorganisationen an die schützende Hand von Zulassungsbehörden. Doch das Ziel ist gleich: Compassionate Use soll leichter möglich werden als bisher.

In Deutschland kämpfen Betroffene mit einem starren Gesetz, das die entscheidende Frage unbeantwortet lässt: Was, wenn die Pharmafirmen die neuartigen Medikamente nicht herausgeben? Derzeit laufen lediglich 14 Compassionate-Use-Programme für Patienten, die nicht mehr warten können. Die Betroffenen leiden an unterschiedlichen Krebsarten, an neurologischen Erkrankungen oder an Infektionen, gegen die kein Antibiotikum mehr hilft.

Es sind Patienten wie der Würzburger Gerald Brandt, 45, der an einer unheilbaren Knochenstoffwechselstörung erkrankt ist. Innerhalb weniger Jahre zog er sich fast 50 Frakturen zu, Mittelfußknochen, Schlüsselbein, Unterarme, Rippen. Er stand kurz vor einem Nierenversagen. Im Mai 2012 erhielt er einen neuartigen Wirkstoff gegen seine Krankheit, lange bevor dieser in Deutschland zugelassen wurde. Brandt sagt: „Ohne Compassionate Use wäre ich heute nicht mehr da.“

In Deutschland sind Compassionate-Use-Programme auf den Websites des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts gelistet. Zwei grundlegende Bedingungen muss ein Medikament erfüllen, um auf ei-

ner der Listen zu stehen: Es muss gegen eine Krankheit wirken, die zum Tod oder zu einer schweren Behinderung führen kann und für die es keine zufriedenstellende Therapie auf dem Markt gibt. Und es muss sich bereits in der klinischen Erprobung befinden. Nur der Pharmahersteller selbst darf einen Antrag beim Bundesinstitut einreichen. Patienten und Ärzte können das Unternehmen darum bitten; doch sie haben nicht das Recht, selbst einen Antrag zu stellen.

Wie viele Menschen ein noch nicht zugelassenes Medikament dringend benötigen, es aber nicht bekommen, das steht auf keiner Liste.

Nur selten treten die Schwerkranken in die Öffentlichkeit, um Hilfe zu finden – als würde sich für kurze Zeit ein Vorhang öffnen. So erfährt die Gesellschaft von tragischen Geschichten, von der Suche nach einem Ausweg aus der Ausweglosigkeit.

Im Frühjahr 2015 hob sich der Vorhang, als auf der Website Change.org eine Petition online ging. „Bitte helft unserer Tochter Hannah zu leben“, stand dort. Hannah, inzwischen zehn Jahre alt, leidet an CLN2, einer Form der sogenannten Kinderdemenz. Die seltene Stoffwechselerkrankung führt zur Erblindung, die betroffenen Kinder verlieren das Laufen und Denken – und sterben früh.

Bislang ist kein Medikament zugelassen, das Hannah Vogel helfen könnte. Das US-amerikanische Unternehmen Biomarin testete zwar einen neuen Wirkstoff, nahm aber keine weiteren Patienten mehr in die bereits laufende klinische Studie auf. Deshalb baten die Eltern Biomarin um einen Einzelheilversuch.

Doch die Pharmafirma lehnte ab.

Der Vorhang stand jetzt weit offen. Familie Vogel wandte sich an Selbsthilfegruppen, 404 685 Menschen unterzeichneten zwischenzeitlich auf Change.org einen Appell an den Pharmakonzern. Hannahs Vater reiste nach London und New York, stellte sich als lebende Litfaßsäule mit einem Schild um den Hals vor ein Gebäude, in dem Investoren von Biomarin zusammentrafen. Es sah aus wie der klassische Kampf David gegen Goliath, der verzweifelte Vater gegen die profitgierige Pharmaindustrie.

Aber so einfach ist es nicht. Die Zurückhaltung der Pharmafirmen liegt auch daran, dass die rechtlichen Hürden in Deutschland zu hoch sind. Das bestehende Gesetz schreibt vor, dass die Unternehmen nicht zugelassene Präparate kostenlos herausgeben müssen. Keine Krankenkasse muss dafür bezahlen.

Hinzu kommt der bürokratische Aufwand: Zu 18 Punkten muss ein Pharmaunternehmen Stellung nehmen, wenn es einen Antrag stellt. Welche Patienten dürfen das Medikament bekommen? Wieso

können die Patienten nicht an einer klinischen Studie teilnehmen? Welche Erkenntnisse gibt es bisher über die Sicherheit des Wirkstoffs?

Behandlungserfolge während eines Compassionate-Use-Programms fließen nicht in die zukünftige Bewertung des Medikaments ein – unerwünschte Arzneimittelwirkungen hingegen schon, auch von solchen Patienten, die gar nicht die strengen Kriterien der Studie erfüllen. Sollte der Wirkstoff einem Patienten ernsthaft schaden, müssten alle laufenden Studien unterbrochen oder sogar beendet werden.

Warum also hätte sich die Firma Biomarin darauf einlassen sollen, Hannah das Medikament vorzeitig herauszugeben? Aus welchem Grund sollte sich überhaupt irgendein Unternehmen auf Compassionate Use einlassen? Eigentlich gibt es keinen Grund. Mitgefühl ist nicht wirtschaftlich. Das deutsche Gesetz macht Patienten zu Bettlern vor Unternehmen.

Es gibt einen Mann, der diesen Skandal nicht akzeptieren möchte. Christian Johnsen, 59, arbeitet als Pfarrer in Berlin. Als Prediger könne man viel über Ideen zur Verbesserung der Welt reden, sagt er, aber wirklich verändern würden sich Dinge nur, wenn man sie anpacke.

Als Student engagierte er sich bei „Christen für die Abrüstung“, später war er Herausgeber eines Magazins in Leipzig, das die Zeit nach der Wende kritisch begleitete. Derzeit leitet er eine bundesweite Hilfsstelle für evangelische Pfarrer. Christian Johnsen ist ein Mann, der sich um viele Baustellen kümmert.

Als ihm eine Bekannte von dem Fall Hannah erzählte, kam eine neue Baustelle hinzu. Er erfuhr, dass weitere Kinder auf dasselbe Medikament warteten, mindestens zehn. Er versuchte zu erreichen, dass die Betroffenen doch noch in die laufende Studie aufgenommen werden.

Und er hörte den Namen eines anderen Kindes, mit einer anderen Krankheit. Miguel Kit Morales-Laubinger aus Hildesheim, heute 22 Monate alt, Diagnose „infantile spinale Muskelatrophie Typ 1“: Muskelschwund in seiner schlimmsten Form. Der Junge muss mehrfach am Tag umgelagert werden, damit er sich nicht wund liegt. Aus seinem Hals ragt eine Atemkanüle. Seit ihr Sohn krank ist, schlafen die Eltern zusammen mit ihm im Ehebett, um sofort reagieren zu können, wenn er zu ersticken droht.

Im Internet schöpfte die Familie Hoffnung: Die Pharmafirma Biogen testet gerade ein Präparat gegen Muskelschwund, das in ersten klinischen Studien tatsächlich zu helfen scheint. Miguels Vater wandte sich an die Klinik, in der die Studie lief. Und erfuhr, dass Miguel wenige Wochen zu alt war, um daran teilnehmen zu dürfen. Kein Arzt, sagen die Eltern heute, habe



WILMA LESKOWITSCH

**Patient Miguel:** Hoffnung im Kampf gegen den Muskelschwund

ihnen von der Möglichkeit des Compassionate Use erzählt.

Dann meldete sich Pfarrer Johnsen bei ihnen. Mit Unterstützung von Selbsthilfegruppen versucht er seither, die Firma Biogen zu erweichen, das Medikament zur Verfügung zu stellen.

Johnsen sieht aber vor allem den Gesetzgeber in der Pflicht, den Zugang zu nicht zugelassenen Arzneimitteln zu erleichtern. Vor wenigen Monaten gab der Pfarrer bei dem Bonner Rechtsprofessor Stefan Huster ein Gutachten in Auftrag. Seit Kurzem liegt das Ergebnis vor. Huster sagt, rechtlich sei es schwierig, Pharmafirmen zu zwingen, Medikamente vorzeitig herauszugeben. Der Professor plädiert deshalb für finanzielle Anreize. Es müsse möglich sein, Pharmafirmen die Kosten für die Behandlung zu erstatten. Dafür sei eine Gesetzesänderung erforderlich.

In Ländern wie Frankreich übernehmen Krankenkassen längst die Kosten für Compassionate-Use-Programme. Pharmafirmen und Krankenkassen können dort einen vorläufigen Preis für ein noch nicht zugelassenes Medikament aushandeln. Dadurch stehen viele neue Medikamente in Frankreich früher zur Verfügung als in Deutschland.

Immerhin will das Bundesgesundheitsministerium das Gesetz zu Compassionate Use demnächst überprüfen lassen. Auch bestätigte ein Ministeriumssprecher, dass es ein Treffen mit Vertretern von Biogen gegeben hat – mit derjenigen Firma also, die Hannah Vogel das womöglich lebensrettende Medikament verweigerte. Es sei in dem

Gespräch um die Voraussetzungen für ein Compassionate-Use-Programm gegangen.

Pfarrer Johnsen sagt, man brauche einen langen Atem, um Dinge zu verändern. Im September soll das Rechtsgutachten veröffentlicht werden. Johnsen glaubt, dass eine Gesetzesänderung Menschenleben retten könnte. Zudem gebe das Gutachten Betroffenen die Chance, gegen Unternehmen zu klagen, die mutwillig die Herausgabe neuer Wirkstoffe verweigern.

Johnsen glaubt an die Macht des Rechts.

Ronald Brus glaubt an die Macht des Marktes. Sobald ein Markt geschaffen sei, sagt der holländische Unternehmer, fänden Pharmafirmen und Patienten zusammen.

Brus beschäftigt mittlerweile 41 Mitarbeiter in 17 Ländern. Sie füllen Compassionate-Use-Anträge aus, verhandeln mit Behörden, organisieren die Lieferung der Wirkstoffe. Ein Jahr nach dem Start arbeitet seine Plattform bereits mit 16 Pharmafirmen zusammen. Sie nimmt Patienten die Bettelei um Medikamente ab und den Firmen die Bürokratie.

Kritiker sagen, Ronald Brus mache Geschäfte mit dem Leiden von Menschen. Wahr ist: Für jedes Medikament, das er vertreibt, verlangt er von den Pharmaherstellern einen Anteil des vorläufigen Preises. Im Gegenzug liefert Brus den Pharmakonzernen wertvolle Gesundheitsdaten über die Patienten. Ein Branchenkenner sieht noch einen weiteren Grund, warum die Pharmafirmen mit Brus zusammenarbeiten: Sie dürfen für noch nicht zugelassene Medikamente keine Werbung machen. Auf der Internetplattform MyTomor-

rows könnten sie dieses Werbeverbot schrittweise umgehen.

„Wir machen keine Werbung“, widerspricht Brus. „Ich habe eine große Idee.“

Anfang Juli tauchte ein weiteres Medikament auf der Liste des Bundesinstituts für Arzneimittel und Medizinprodukte auf: Biomarin, die Firma, die Hannah Vogel das Medikament gegen Kinderdemenz seit eineinhalb Jahren verwehrt, ist nun doch zu Compassionate Use bereit. Es ist nicht sicher, ob der Wirkstoff Hannah noch helfen kann.

Auch für Miguel aus Hildesheim gibt es Hoffnung. Das Unternehmen Biogen erklärte auf Anfrage des SPIEGEL, sie werde ein Compassionate-Use-Programm starten, noch in diesem Jahr. Und lässt sich doch eine Hintertür offen: Zuvor müsse nachgewiesen sein, dass der Wirkstoff gegen Muskelschwund wirklich helfe und sicher sei.

Hannah und Miguel – am Ende werden die Konzerne mit der Hilfe für die Kinder so lange gewartet haben, bis die Zulassung für die Mittel ohnehin so gut wie sicher ist.

Das Medikament gegen Lungenkrebs, mit dem Ronald Brus seinen Kampf begann, ist am 2. Oktober 2015 in den USA zugelassen worden. Keytruda ist dort seither frei verkäuflich, jeder Patient, dem es verschrieben wird, kann es erhalten.

Ronald Brus aber hat es nicht geschafft, den Wirkstoff rechtzeitig für seinen Vater zu beschaffen.

Piet Brus starb Ende 2012, vier Tage nach Weihnachten.

Vivian Pasquet, Martin Schlak

► year. In April 2015, an underwater volcano laden with OOI instruments erupted, just as scientists had predicted — but the live data were not yet flowing to the wider scientific community.

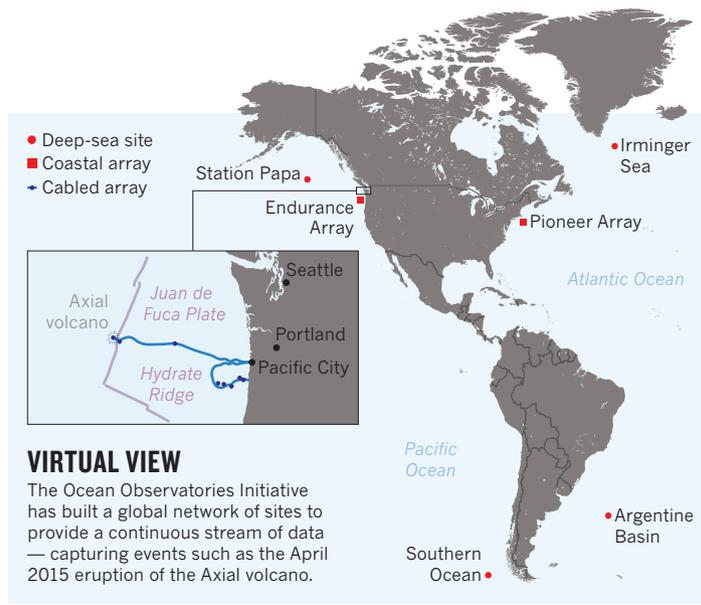
Now, about 85% of OOI data are available in real time on the project's website, with the percentage growing every week, says Greg Ulses, the current programme director at the Consortium for Ocean Leadership. The information — on factors such as temperature and salinity — streams from more than 900 sensors at the 7 sites.

The OOI consists of one high-tech cable on the tectonically active sea floor of the northeast Pacific Ocean, together with two lines of oceanographic instruments — one off the US east coast and the other off the west coast — and four high-latitude sites, near Greenland, Alaska, Argentina and Chile. Each array involves a combination of instruments, from basic salinity sensors to sophisticated underwater gliders.

The NSF built the network as a community resource, hoping to stimulate an era of virtual oceanography in which scientists explore real-time data sets open to all (see 'Virtual view').

"We know the data are valuable," says Lisa Campbell, a biological oceanographer at Texas A&M University in College Station. "How to implement it is what we're working on."

Those involved in the OOI's painful birth are happy to see it working at last. "When I finally got through and saw the real-time data, I shouted so loud someone had to come down the hall and close the door," says Glen



### VIRTUAL VIEW

The Ocean Observatories Initiative has built a global network of sites to provide a continuous stream of data — capturing events such as the April 2015 eruption of the Axial volcano.

Gawarkiewicz, a physical oceanographer at the Woods Hole Oceanographic Institution in Massachusetts.

The array off the coast of Massachusetts has already captured some unprecedented observations, he says. In 2014, it measured air-sea fluxes when a hurricane passed overhead. The following winter, it measured dramatic shifts in the boundary at which shallow waters interact with deep ones. "That has tremendous practical implications, because there's a lot of commercial fishing in that area," Gawarkiewicz says. Using OOI data, he is now working with local fishers to share real-time information on changes in temperature and currents.

The west-coast array has studied a warm blob of water linked to weather patterns that are strengthening the ongoing drought in California. And in the North Atlantic, off the coast of Greenland, OOI scientists have coordinated their measurements with those of

others, such as an international programme to measure heat flow in this key region. "These are high-scientific-value sites that we have dreamed about, and now we have occupied them," says Robert Weller, a physical oceanographer at the Woods Hole Oceanographic Institution.

But the OOI's future remains murky. A 2015 review of US ocean-science priorities suggested that the programme's operational budget should be slashed by 20%, to around \$44 million a year. Yet each of the arrays must be serviced every year or two to replace broken instruments and install new ones.

The NSF has not yet decided how it will save that 20%.

Later this year, the agency will solicit bids to manage the OOI for the next five to ten years. Who responds, and with what suggestions, will help to determine what gets cut. "We built this thing, and will be funding operations for what the community feels is best," says Murray.

Ultimately, there is no metric for what constitutes a successful OOI. Ulses says that the project needs to run for a full year before managers can assess which scientists are using which data, and how stable and successful the data streams are.

Weller would like to see a set of OOI measurements become as iconic as the records of atmospheric carbon dioxide levels taken at Mauna Loa, Hawaii, since the 1950s. "On any given day, I step back," he says, "and am still sort of amazed that it's all out in the water and most of it's working." ■

SOURCE: OOI

## BIOMEDICINE

# Panel tackles 'compassionate use'

*Companies pressured by social-media appeals seek fair way to allocate last-ditch treatments.*

BY SARA REARDON

Nancy Goodman wanted to spend as much time as possible with her dying child. But even as ten-year-old Jacob's brain cancer worsened, Goodman spent months contacting pharmaceutical companies that were developing drugs that might help him.

'Compassionate-use' laws in the United States allow pharmaceutical companies to provide unapproved drugs to patients in desperate need, but many firms provide little or no information on how to request these treatments. They are often reluctant to supply drugs

in response to such pleas, especially if drug stocks are limited, although media campaigns on behalf of individual patients can sometimes embarrass firms into providing unapproved treatments. Anecdotes suggest that money and connections are also influential.

Now, ethicists and medical experts are testing what they hope is a fairer system to distribute drugs in short supply. The approach, presented on 6 June at the American Society of Clinical Oncology meeting in Chicago, Illinois, is inspired by the method used to prioritize organ transplants. In a test case, researchers worked with Janssen Pharmaceuticals to

determine how to distribute limited supplies of daratumumab, an experimental drug intended to treat multiple myeloma.

The 10-person panel combed through 76 anonymized applications to determine how likely the drug was to work for each person, ultimately approving 60. "It's hard to say no, because people die," says Arthur Caplan, a bioethicist at New York University's Langone Medical Center who is leading the effort. But he says that a systematic approach could help companies to make unbiased decisions.

In Goodman's case, six of the eight companies that she contacted never responded. The

other two declined to give her son their drugs because the treatments had never been tested in children. Jacob Goodman died in 2009, and his mother went on to found the advocacy group Kids v Cancer in Washington DC.

There are many legitimate reasons that companies might refuse to provide unapproved drugs, says Aaron Kesselheim, who studies health-care ethics at Brigham & Women's Hospital in Boston, Massachusetts. People who request such treatments are often very ill, and companies worry that their deaths while receiving the drug would reduce the compound's chances of approval from the US Food and Drug Administration (FDA). Giving patients access to experimental drugs could also discourage them from enrolling in controlled trials that might assign a placebo, and would leave less drug available for use in the trial.

"These requests are some of the most difficult decisions I face as a physician," says Amrit Ray, chief medical officer of Janssen in Titusville, New Jersey. "It's a trade-off we have to consider carefully."

Since 2014, 28 US states have enacted 'right-to-try' laws, which allow companies to provide drugs to patients without involving regulators. Caplan calls these "feel-good" laws, because the FDA approves most of the compassionate-use requests that it receives. (It is not clear how many applications are denied by companies and never reach the FDA.)

Vickie Buenger, president of the advocacy group Coalition Against Childhood Cancer in Philadelphia, Pennsylvania, says that right-to-try statutes contribute to patients' misunderstanding about the factors that go into a decision to supply or deny access to a drug. "It implies that companies and the FDA are either angels of mercy if they come through, or devils who have no compassion if they withhold it."

This lack of clarity, and poor communication by companies, has led many patients and their families to launch social-media campaigns to secure unapproved drugs.

Perhaps the most famous case came in 2014, when the family of seven-year-old Josh Hardy began a Facebook campaign for an unapproved antiviral drug called brincidofovir to treat a life-threatening infection. Its manufacturer, Chimerix of Durham, North Carolina, had declined, on the grounds that giving the drug to Josh — and any subsequent petitioners — would leave less of the compound



Josh Hardy received an experimental drug after his family launched a massive social-media campaign.

available for an ongoing clinical trial. Within days, the Facebook page and Twitter campaign #savejosh were featured on national television. Chimerix quickly created a small clinical trial with Josh as its first patient.

"Every single CEO woke up the next morning and said, 'Oh my gosh, that might happen to me,'" says Elena Gerasimov, who directs a programme at Kids v Cancer that helps

**"These requests are some of the most difficult decisions I face as a physician."**

parents of children with cancer to petition companies for drug access. (The FDA is attempting to make this process easier. On 2 June, it released new forms to simplify the filing of compassionate-use appeals.)

Former Chimerix chief executive Kenneth Moch says that dozens of companies have since enlisted him as an adviser on such issues. His advice is simple: every company should create a transparent system to handle compassionate-use requests, guided by the FDA. That is in line with the advice of the Biotechnology Innovation Organization, an industry group in Washington DC that encourages its members to develop clear policies to explain whether they provide expanded access and to help physicians to request drugs. "That's the least we can

do, to facilitate people being able to contact us," says Kay Holcombe, the group's senior vice-president for science policy.

Caplan and Ray plan to test their system on another treatment later this year — possibly a mental-health drug or a childhood vaccine. Caplan hopes that more companies will adopt the approach, and imagines eventually creating a compassionate-use consulting panel to aid small companies.

Moch cautions that the approach might not be appropriate for every drug or company, but he likes how it helps to level the playing field. "Had Josh been a 37-year-old guy who kicked his dog and smoked, he wouldn't have gotten the same support as a lovely seven-year-old boy," he says.

Patient advocates also support Caplan's system for distributing drugs. "Putting it in the hands of people who understand the drug's possibilities is a reasonable thing," Buenger says.

But many also want the FDA to create incentives for companies to provide drugs for compassionate use. Until that happens, or until companies adopt programmes such as Caplan's, social-media campaigns and other public appeals may be some patients' only option. "I'd do it," Goodman says. "I'd do anything to save my kid — anything to give Jacob a few more months." ■

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# Vom Recht auf Leben

Hannah und Miguel sind schwer erkrankt. Es gibt Medikamente, durch die sie gerettet werden können. In einem Fall wird das Mittel unter Verschluss gehalten. Im anderen Fall gibt es Hoffnung

VON CHRISTINA BERNDT

Gerade ist Hannah wieder schlimm gefallen. Große, blaue Pflaster trägt sie an beiden Händen. „Man kann sie kaum noch alleine gehen lassen“, sagt ihre Mutter Stefanie Vogel. „Sie stolpert viel und fällt oft.“ Allein die Treppe runtergehen? Unmöglich. Noch trägt Vater Michael Vogel die Zehnjährige. Aber bald wird die Familie einen Treppenlift in ihr Häuschen in der Nähe von Bad Tölz einbauen müssen. Dass Hannah ihn selbst bedienen kann, ist unwahrscheinlich: Spürbar lässt auch ihr Geist nach. Neulich waren Ferien in Bayern. „Da fragte sie alle paar Minuten, wann wir zur Schule fahren“, erzählt die Mutter. „Und wenn Freunde da sind, vergisst sie selbst die.“

Mit jedem Tag verliert Hannah mehr von sich und der Welt. Die Zehnjährige hat Kinderdemenz, genauer: NCL2. In ihrem Gehirn häufen sich wegen eines Gendefekts giftige Stoffwechselprodukte an. Deshalb sterben ihre Nervenzellen ab, und mit jedem Stolpern, mit jeder wiederkehrenden Frage zeigt sich der fortschreitende Verfall. Dabei zusehen zu müssen, ist für die Eltern kaum zu ertragen. Noch dazu, wo es eigentlich ein Medikament gibt, das Hannahs Krankheit aufhalten könnte. Und das, wie neueste Daten zeigen, mit unglaublicher Kraft.

Seit fast einem Jahr kämpfen Stefanie und Michael Vogel nun schon dafür, dass Hannah das Medikament namens BMN 190 bekommt, das die kalifornische Biotech-Firma Biomarint entwickelt hat. Zwar ist es noch nicht zugelassen. Aber die Abgabe wäre rechtlich trotzdem möglich – im Rahmen eines Härtefallprogramms, von dem auch andere NCL2-Kinder profitieren könnten. Es wäre ein „Compassionate Use“, ein Gebrauch aus Barmherzigkeit, doch die Firma zeigt sich hartherzig.

Wie sehr BMN 190 Hannah helfen könnte, zeigen Daten, die nun während eines Symposions in San Diego präsentiert wurden. Die Wirkung ist demnach überwältigend: Bei 20 der 23 Kinder, die BMN 190 ein Jahr lang bekamen, schritt die Krankheit deutlich langsamer fort, 15 Patienten stabilisierten sich sogar, wie die Studienleiterin Angela Schulz vom Uniklinikum Hamburg-Eppendorf berichtete: „Sie behielten ihre Fähigkeit zu laufen und zu sprechen.“ Obwohl BMN 190 alle zwei Wochen ins Gehirn injiziert werden muss, traten kaum Nebenwirkungen auf.

Doch für Biomarint ist das kein Anlass, die Arznei herauszugeben. Die Firma zeigt sich ausgeruht: In drei Monaten werde man die Zulassung beantragen, diese werde hoffentlich Anfang 2017 erteilt. Eventuell werde man kurz zuvor, etwa ab dem dritten Quartal 2016, einen „Early Access“ anbieten. Die Zusage bleibt vage. Klar ist nur: Den frühen Zugang werden nicht alle bekommen. Das Programm werde „in Zahl und Reichweite“ limitiert, schreibt Biomarint. Dabei geht es nicht darum, Millionen Patienten zu behandeln: NCL2 ist eine extrem seltene Krankheit. In Deutschland gibt es nur etwa 30 Kinder mit dieser Demenz. Biomarint schätzt die Zahl der Kinder in seinem Geschäftsgebiet selbst auf 1200 bis 1600.

Das Leid, das ihnen erspart werden könnte, hält niemand auf. Die Kinder müssen warten – obwohl selbst Angela Schulz als behandelnde Ärztin die Firma schon um ein Härtefallprogramm gebeten hat. Auf ihrer Warteliste stehen zahlreiche Patienten, denen Behinderungen womöglich erspart blieben, wenn sie nun behandelt würden. Jede Woche, die vergeht, nimmt den Kindern Chancen. Bis zur Zulassung von BMN 190 werden einige von ihnen nicht mehr sehen und sprechen können, andere werden sterben.

Hannahs Eltern haben alles versucht. Ihre Petition auf [change.org](http://change.org) hat mehr als 400 000 Unterstützer gefunden. Sie sind in Talkshows aufgetreten und haben vor Biomarint ebenso wie bei Investorentreffen in London und New York protestiert. Auch an Politiker haben sie geschrieben, darunter Bundesgesundheitsminister Hermann Gröhe (CDU). Der ließ lange nichts von sich hören, bis er einen Tag vor Weihnachten in einem Brief bedauerte, dass er nichts tun könne. Auch der SZ teilte er mit: „Die Entscheidung liegt allein beim pharmazeutischen Unternehmen.“



Hannah, 10, hat Kinderdemenz (Foto oben). Eine neue Arznei würde ihr viel Leid ersparen – doch die Firma will das Mittel nicht herausgeben. Miguel, 17 Monate (unten), könnte mehr Glück haben.

FOTOS: JAKOB BERR, WING KIT LEE

„Das ist es ja gerade, die Pharmafirmen sind zu nichts verpflichtet“, ärgert sich Christian Johnsen. Der Pastor setzt sich als Leiter der Hilfsstelle für evangelische Pfarrer für einen leichteren Zugang zu experimentellen Medikamenten ein. Aus freien Stücken bieten nur wenige Firmen Compassionate Use an. Derzeit gibt es hierzulande 14 solcher Programme, in Frankreich sind es mehr als zehnmals so viele – wohl auch, weil dort Krankenkassen die Kosten übernehmen. So stehen Medikamente Schwerstkranken im EU-Ausland fünf bis sechs Monate eher zur Verfügung als in Deutschland. „Zeit, die über Leben und Tod entscheiden kann“, sagt Johnsen, ein großer, schlaksiger Mann, der das Kunststück vollbringt, zugleich viel reden und gut zuhören zu können.

Aber haben die Kinder nicht ein Recht auf eine Medizin, die ihr Leben retten kann? Ist es womöglich unterlassene Hilfeleistung, ihnen eine Behandlung zu verweigern? Um das zu klären, hat Johnsen die Hilfsstelle den Auftrag für ein juristisches Gutachten in der *Neuen Juristischen Wochenschrift* und im *Pfarrerblatt* ausgeschrieben. Allerdings nutzt auch Biomarint die Ethik als Argument: Man Sorge sich, dass ein Härtefallprogramm die Zulassung des Medikaments aufhalten könne, schreibt die Firma. Wenn dabei wieder Erwartungen etwas schiefeht, gefährde das den Zugang zu BMN 190 „für Patienten in der ganzen Welt.“

Allerdings ist in der Praxis noch nie eine Zulassung durch Compassionate Use

gefährdet worden, wie das Bundesinstitut für Arzneimittel und Medizinprodukte betont. Und selbst wenn: Darf man das Lebensrecht von Kindern wie Hannah mit Blick auf die Lebensrechte anderer Kinder beschneiden? Es ist das klassische Dilemma von der Weiche, die man umstellen

Und doch können Patienten derzeit nur von Glück reden, wenn eine Firma zur vorzeitigen Abgabe eines lebensrettenden Medikaments bereit ist. Miguel aus Hildesheim könnte dieses Glück beschieden sein. Der 17 Monate alte Junge leidet am Muskelschwund SMA. Die Krankheit bedroht sein Leben, weil er ohne Maschine nicht mehr atmen kann. Auch für ihn befindet sich ein Medikament in ersten Studien. Aber die Arznei stammt von einer anderen Firma, Biogen. Nicht Biomarint.

Miguels Krankheit wurde festgestellt, als er ein Baby war. Anders als andere Kinder hielt er nie selbstständig seinen Kopf, Arme und Beine hingen schlapp herunter. Der Arzt wurde regelrecht böse, als die Mutter ihren Sohn trotzdem nicht sterben lassen wollte. Doch für Melissa Morales-Laubinger und ihren Freund Wing Kit Lee stand fest: Wenn jemand über das Leben von Miguel entscheidet, dann nur Gott. Nicht sie, nicht der Arzt und sicher keine Pharmafirma. „Sehen Sie mal, welchen Willen er hat, er will doch leben“, sagt die Mutter, die selbst voller Leben ist. Ihre dunklen Augen leuchten, sie lächelt viel, obwohl das Thema, über das sie spricht, von einer kaum erträglichen Schwere ist.

Für ihre Familie hat Pfarrer Johnsen schon viel erreicht. Die Firma Biogen ist zu Compassionate Use bereit: „Wir werden ein solches Programm so schnell wie möglich auflegen“, sagt der Konzernsprecher. Und dann sagt er noch einen Satz: „Wir sind uns der Dramatik bewusst. Das ist doch jeder, der Kinder hat!“



Die Entscheidung

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Hermann Gröhe (CDU),

Bundesgesundheitsminister,

sieht sich nicht

in der Lage zu helfen

könnte, damit ein führerloser Zug nur einen und nicht fünf Menschen erfasst. Die Rechtsprechung ist eindeutig: Man darf Einzelne nicht opfern, wie das Bundesverfassungsgericht in seinem Flugzeugabsturz-Urteil 2006 entschieden hat.