feature

The unique status of first-in-human studies: strengthening the social value requirement

Michelle G.J.L. Habets, habets@law.eur.nl, Johannes J.M. van Delden and Annelien L. Bredenoord

For clinical research to be ethical, risks need to be balanced by anticipated benefits. This is challenging for first-in-human (FIH) studies as participants are not expected to benefit directly, and risks are potentially high. We argue that this differentiates FIH studies from other clinical trials to the extent that they should be given unique status in international research ethics guidelines. As there is a general positive attitude regarding the benefits of science, it is important to establish a more systematic method to assess anticipated social value to safeguard participants not only from enrolling in risky, but also in futile trials. Here, we provide some of necessary steps needed to assess the anticipated social value of the intervention.

Introduction

The recent tragedy in Rennes is a reminder of the dangers of first-in-human (FIH) studies. After taking the experimental, candidate drug BIA10-2474, designed to deal with pain, mood disorders, and anxiety, one healthy volunteer died and four other men may have permanent brain damage. Although tragic events like these are fortunately rare, it is indisputable that research participants in FIH studies are exposed to potential (serious) harm, both predictable as well as unexpected. FIH studies form the foundation of the bridge that crosses the translational valley of death: 'the widening gap between advances in basic science and the practical application of that knowledge' [1]. They are *designed* to evaluate the risks and tolerability as well as the Maximum Tolerated Dose (MTD) of a drug or intervention. In subsequent trials, risks are lower, because severe harm with a high rate of recurrence will, in all likelihood, have been uncovered in the FIH study.

Until the disaster in the Northwick park trial in 2006, where six healthy volunteers exposed to TGN1412 were hospitalized with multi organ failure, there was a lack of specific regulatory guidance on FIH trials [2]. The tragic outcome of this FIH study was a wakeup call for pharmaceutical companies and regulatory agencies. The cytokine storm induced by this monoclonal antibody made it clear that methods to assess risks for traditional small molecule drugs were not sufficient for new biologics. Several regulatory guidelines specific for FIH studies have been issued after the Northwick park event [3–5] to standardize the identification and mitigation of potential *risks* (known probabilities of harm with a certain magnitude) and *uncertainties* (unknown probability of known risk). However, this is more difficult to determine for complex innovative interventions, such as biologics and emerging technologies. For example, pluripotent stem cells-derived interventions bring additional concerns because of the *ex vivo* cultivation of cells, possibly leading to contamination of cells or genetic aberrations in the cell line due to the selection procedure of rapidly proliferating cell lines. Moreover, accidental transplanted non-differentiated stem cells can cause teratomas. In addition to these risks and uncertainties, for innovative health interventions, unpredictable adverse reactions or 'unknown unknowns' (*ignorance*) may also occur at a higher rate [6]. Due to a lack of precedent for these complex innovative interventions, research subjects are exposed to more uncertainty and ignorance. Additionally, there is an increased risk because of the invasive and often irreversible insertion of these innovative interventions, and the limited predictability of animal models [7].

Features • PERSPECTIVE

Although we cannot indiscriminately bring all FIH studies under the same umbrella, when examining complex innovative interventions in FIH studies, greater precautionary measures should be exercised in the design of the FIH study compared to subsequent trials.

For research to be ethical, risks need to be balanced by benefits [8]. However, FIH studies are not designed to provide a therapeutic benefit for research participants, which is most evident when healthy volunteers are enrolled. Therefore, although it might not be excluded that a medical benefit does occur, this cannot be the justification for enrolling individuals. Instead, the justification needs to be found in the anticipated social value of the intervention [8,9]. Unfortunately, no guidance is given in ethical and regulatory guidelines on how to assess the anticipated social value [9]. Our aim in this paper is to provide some of the necessary steps needed for assessing the anticipated social value of interventions.

Balancing potential harm and anticipated social value in FIH studies

Similar to risks, uncertainty exists whether conducting FIH studies will lead to any benefits in future. However, whereas for uncertainty relating to risks, Research Ethics Committees (REC) and researchers usually use the precautionary principle, for uncertainty in benefits of science, a general disposition exists 'towards hopefulness or confidence of success', which Barke has labelled the sanguinity principle [10]. This principle is the counterpart of the precautionary principle. Whereas for risks, the burden of proof to show that harm will *not* take place lies on the individuals that want to do the research; for benefits, the burden of proof to show that science will *not* provide a *benefit*, seems to lie on the shoulders of those who would reject doing the research [10]. Indeed, researchers, but also the public, have a positive view on the societal benefits of medical science [10]. A survey in the US in 2008 found a positive public attitude about science and technologies, across all demographics, and more than 50% of the public agreed with the statement that the benefits of scientific research have strongly outweighed its harmful effects, and 87% expressed support for government funding [11].

In contrast to this positive attitude, based on recent data, we can actually be fairly certain that most interventions tested in clinical trials will *not* lead to any societal benefit. Indeed, the success rate of interventions entering FIH studies is very low; only about 8–10% of interventions in FIH studies lead to market authorization [12,13].

Incidentally, it has been estimated that less than 8% of these approved drugs offer an increased therapeutic benefit over existing drugs [14]. Many participants thus enrol in trials that will not lead to benefits for society; in addition, one study demonstrated that about 15% of marketed authorized drugs are more harmful than beneficial [14]. Whether these numbers are widespread is not known, however, a worrisome report from the US Government Accountability Office in January 2015, revealed that '. . .[proble-[problems]. . .have prevented the FDA from publishing statutorily required reports on certain potential safety issues and post market studies in a timely manner, and have restricted the agency's ability to perform systematic oversight of post market drug safety' [15]. As post market evaluation of medical interventions is apparently not up to date, exact knowledge on how many interventions are harmful is lacking.

At this point, one could of course argue that there are many different ways, besides market authorization of the tested intervention, in which a trial can be valuable. For example, Kimmelman has distinguished various ways a FIH study can be valuable: it can motivate further preclinical studies (reciprocal value); it can lead to modifications in the trial itself when repeated (iterative value) and it can even provide useful knowledge for other interventions in the drug pipeline (collateral value) [16]. We do not deny that important knowledge can be obtained from FIH studies independent of eventual market authorization of the intervention; however, when finding a justification for enrolling humans in a FIH study it should not be mere knowledge. The risks and uncertainties to the research participants should be balanced by the anticipated social value *of the intervention*. It is the intervention that will benefit future patients. Moreover, this is a prospective evaluation; what is important is how the *intervention* may change the lives of (future) patients. Any possible, unforeseen, important knowledge should not weigh in the decision to approve a trial in a prospective evaluation.

By design, FIH studies assess potential harm to future patients, and by design, they rarely provide a therapeutic benefit to participants, and in reality, they most often do not lead to future market authorization of the examined intervention. Although subsequent trials may neither provide a benefit to participants (nor lead to market authorization), what makes these trials different, is the *expectation of a possible benefit* to the participant. Researchers need to be agnostic about future improvement or decline in patients' wellbeing, when comparing a new intervention

with the standard of care. Phase II and III trials are designed to allow for *patient*-participants (never healthy volunteers) to benefit. Potential harm should be balanced with the anticipated social value of the intervention, and potential therapeutic benefit. Moreover, in theory, the risks are reduced in phase II and III trials. For these reasons, FIH studies are ethically distinct from other trials, and we believe making this explicit in guidelines on ethical principles is important for two reasons; first, FIH studies should be assessed differently by researchers and RECs; second, FIH participants are in need of additional protection, due to the type of research. Thus, although specific regulatory guidance is available to standardize the identification and mitigation of potential risks in FIH studies [3–5], we argue for recognizing the unique status of FIH studies among clinical trials in international guidelines on ethical conduct in clinical research. In a similar manner, as for example, CIOMS has guidelines specifically for women, children and adolescents, and vulnerable persons, we argue for a separate guideline for FIH study participants, as they too, are more vulnerable than participants in subsequent trials [17].

Participants need additional safeguarding

In the following sections we will discuss several ways to safeguard research participants in FIH studies. Of course, risk assessment and risk minimization is the most vital way to protect participants. However, here, we are interested in ways to safeguard humans from enrolling in futile FIH studies. For that purpose, we will first provide some necessary, although not exhaustive, steps to assess the anticipated social value of the intervention. This is important because RECs have no common language to consider nor a common approach to assess these benefits in human research [18], and simultaneously, they will also be led by the sanguinity principle (they are hopeful of success).

First safeguard: accurate assessment of the anticipated social value of the intervention

When assessing the anticipated social value of the intervention, we need to follow at least the following three steps.

Step 1. Estimating the pharmacological effect in humans

In a first step, researchers and RECs need to *estimate* the nature and magnitude of the pharmacological (pharmacodynamics and pharmacokinetics) effect the intervention will have in humans. This prediction will be made in

first instance by studying the preclinical data on efficacy. Correct evaluation of preclinical data is very important. However, increasingly, reports are published about the inadequacy of preclinical research, for example, methodological flaws [19] such as lack of randomization and blinding [20] and inadequate statistical analysis in reporting [7]. Publication bias of preclinical trials has also been found [19]. Often, disciplines have a preferred animal species based on costs, ease of use, habit, and reproductive capacity [21].

Several suggestions have been made to improve the predictability of animal studies and thus to provide additional safeguards for FIH participants; for example having a central register for animal trials, in a similar manner as is already the case for clinical trials [7]; minimum standards for range and quality of animal data before translation can take place [22]; rigorous methods such as blinding and random assignment [19,22]; broadening the preclinical evidence by looking at reference classes [23], routinely conducting systematic reviews [24], but also plain transparency, standardization, uniform reporting, replication, as well as unbiased selection and publication of preclinical data [20,24–28]. Simultaneous, however, the predictability of animal models is much less reliable for emerging technologies, such as nanotechnology, than for traditional molecules [27]. Possibly, iPSC cell tissue could help predict the pharmacodynamics and pharmacokinetics of preclinical interventions in humans. As these cells are not only human, but can also be patient specific, they will be good predictors for the impact of interventions on cells.

After evaluating the preclinical data to estimate the nature and magnitude of efficacy of an intervention in animal models, Kimmelman and Henderson argue that the *likelihood* of efficacy inferred from preclinical trials should be adjusted by comparing the intervention to similar interventions in the same reference class that have already been tested in FIH studies [30]. For example, in the case of stroke, none of the interventions studied in animal models were shown to be efficacious in human trials. So far, this has not led to changing the commonly used animal model for preclinical research in stroke [18,31]. When researchers and RECs need to assess a stroke intervention, they should take this information into account [30]. Results of preclinical trials therefore need to be publicly available; compulsory publication in a database would give researchers, RECs, and the scientific community as a whole, an opportunity to scrutinize these data before translation takes place.

As RECs have difficulties interpreting elaborate preclinical trial data [32], it may be well worth designing training programs for REC members [29]. These trainings could be focussed on decision-making in data poor settings in the presence of uncertainty [33]. Principles for facilitating decision-making need to be developed. This could be done by establishing specialized working groups within the FDA or EMA [29].

Step 2. The anticipated clinical improvement of the patient

Assuming that the intervention will be efficacious, the next step is to assess whether the intervention will also lead to a clinical improvement for patients. Even if efficacy in surrogate endpoints is expected, based on preclinical data, this may not lead to an improvement in patients' wellbeing. A reduction in tumour size may, for example, not lead to an improvement in quality of life, or life extension. In addition, assessing a clinical improvement consists of weighing the anticipated pharmacological effect against factors that may prevent the intervention from improving (future) patients' wellbeing. The most important cause may be adverse drug reactions. For example, the infamous drug thalidomide, used in the 50's to treat morning sickness, caused thousands of disabled babies to be born. The drug was banned from the market; however, at the moment, thalidomide seems a promising drug for children with TB meningitis resistant to routine medication [34]. For these patients, the risks of adverse side effects may be worth taking, as the disease can be fatal (and pregnancies while on the drug, can be avoided). Unfortunately, we often do not know the risks.

Other aspects that are important, and may be predictable, are the duration of the pharmacological effect, as well as the ease of use. Can we predict by, for example, the manner of applying the intervention whether patients will want to use the drug? For life saving medication, burdens and side effects can be high; for other medication, many factors are relevant to patients when deciding whether they will make use of a market-approved medication.

Step 3. The anticipated social value of the intervention

Once clinical improvement is anticipated, it needs to be assessed on a societal level. As social value is an ambiguous concept, we have proposed in previous work to limit the concept of social value to the *nature and magnitude* of the improvement the intervention is expected to have on the wellbeing of patients, individuals in

society, or society [9]. Although knowledge gained from clinical trials can be very important, we believe that to enrol participants in high-risk FIH studies, a reasonable expectation of social value of the intervention needs to be present *before* enrolling them. We cannot justify FIH trials retrospectively. Ultimately, it is the intervention or the application of the knowledge that will have value for society. The anticipated social value is the clinical benefit to patients, *relative* to the already market approved availability of alternative interventions, number of patients, disease severity, and coverage in health insurance.

Although it is the task of both researchers and RECs to *weigh* possible harm to research participants with anticipated social value, outside of this risk-social value analysis, it is hard to determine what has anticipated social value. We have previously argued, that it is the public at large that needs to decide what contributes to social value. Is it number of patients affected by a disease, severity of disease, quality of life or other aspects? This could be done, for example, through funding agencies that set up (part of) their research agenda based on political decisions regarding societal challenges that require research programs [9].

It is important to be aware that we have not assessed the FIH study itself, only the maximum value that (future) patients or society can gain from the intervention that will be examined. The evaluation of the intervention precedes the assessment of the trial, as it is a prerequisite that the intervention is anticipated to have social value.

Of course, it is also important to evaluate the trial itself; what is the translational prospect of the study; and what is the validity of the study design, but we have discussed this elsewhere [9].

Second safeguard: transparency of data

A second approach to prevent research participants from enrolling in futile FIH studies, is maximizing knowledge on trials and interventions, and thus abandoning the secrecy of safety and efficacy data by pharmaceutical companies, researchers and the FDA. The US Food and Drug Administration Amendments Act only require results of clinical trials examining *FDA approved interventions*, to be published on clinicaltrials.gov, one year after the end of the trial. Compliance with this is extremely low. STAT investigated compliance of pharmaceutical companies in 9000 trials in clinicaltrials.gov and found only two entities that complied with reporting requirements more than half of the time (http://www.statnews.com/2015/12/13/

clinical-trials-investigation/). Although transparency for its own sake could be an ethical requirement, it is also important for protecting research participants.

In the aftermath of the tragic events in Rennes, it became clear that multiple pharmaceutical companies had (already) evaluated FAAH1 inhibitors as possible treatments for pain, mood disorders, and other medical problems; for example, Pfizer has tested their FAAH1-inhibitor PF-04457845 in six clinical trials who are all either completed or terminated (clinicaltrials.gov (PF-04457845)); Ironwood Pharmaceuticals, Inc. has completed one trial (clinicaltrials.gov (IW-6118)); and Sanofi completed one, and terminated another trial (clinicaltrials.gov (SSR411298)) [35]. Unfortunately, on clinicaltrial.gov no results can be found yet, but see [36,37]. Although there is a general duty to register clinical trials, some of the policy Acts make exceptions for phase I trials [38]. As a consequence, it is possible that more individuals than necessary may enrol in trials due to repetitive studies, exposing them to potential risks. Moreover, with the current policy, researchers cannot learn from each other's negative results, or build upon others' knowledge, delaying scientific understanding. This can lead to individuals enrolling in futile trials, in spite of the evidence of non-efficacy being available. In addition, keeping data secret breaks the social contract, a hypothetical agreement, with research participants who may have enrolled for altruistic reasons (Michael McDonald, pers. commun.). Last, the lack of an obligation to make results public, has led to a well-recognized problem of biased publication of data of clinical trials.

Recently, the International Committee of Medical Journal Editors proposed plans for making data sharing of clinical trials a requirement for publication in ICMJE member journals, and all other journals that will follow their recommendation [39]. These positive developments may be undermined by the increase in industry sponsorship, as this is associated with changes in the disclosure behavior of academic researchers. These researchers are 'subject to more stringent contract terms that restrict publication disclosure through delay and secrecy' [40]. Moreover, published studies sponsored by industry are more likely to have industry-favoring outcomes [41,42].

At the very least FIH studies should require registration in a publicly available database, as is already the case for phase II, III and IV. Also compulsory for other phases since the US Food and Drug Administration Amendment Act of 2008, is revealing sponsor-imposed publication restrictions, when employees other than the sponsor, publish results [43]. Unfortunately, these publication restrictions are now made *after* trial results are published. We agree with Stretton and colleagues that these restrictions should be made available before participants enrol, in the informed consent form [43]. This is necessary for participants to make an informed decision. Indeed, the general lack of transparency in informed consent forms about whether results are required to be published or can be kept quiet, could be seen as unethical.

Third safeguard: direct benefits in FIH studies

A last recommendation to safeguard research participants, is for FIH trials to initiate testing for efficacy, besides the potential risks. Especially for interventions of currently untreatable diseases that give rise to a high morbidity or mortality, it may be desired to design studies to *allow* at least a minimal chance of direct benefits. This can be done by using what is expected to be a therapeutic dose, instead of starting with sub therapeutic levels, and by enrolling patients able to benefit, instead of refractory patients. This would be a way to circumvent participants from enrolling in trials for the prospect of generating scientific knowledge alone, which, we have argued, can never justify exposure to risks and burdens of invasive interventions. Indeed, patients with an open therapeutic window have the possibility to benefit therapeutically, whereas healthy research subjects and often, refractory patients, cannot.

Elsewhere, we have provided arguments for assessing, as well as restricting, efficacy in FIH studies (submitted). Briefly, trade-offs can exists between, for example, the optimal trial design to provide a potential direct benefit and the optimal trial design to reduce risks. For instance, in a phase I study with Amyotrophic Lateral Sclerosis (ALS) patients, the choice was made to inject neural stem cells within the lumbar spinal cord, as this was safer than injecting them at the level of the cervical spine, which would have been able to provide the participants the potential to benefit [44]. Safety of the participants should always stay the primary focus of researchers. In addition, testing efficacy as an additional endpoint should never be used to evade the stricter regulation of non-therapeutic trials (submitted). Only under specific circumstances should efficacy be examined as an additional endpoint to safety in FIH studies.

Conclusion
Here, we have demonstrated that the ethical challenges of FIH studies are more complex than other clinical trials, and, as a consequence, FIH studies should be accorded unique status in ethical guidelines. Moreover, research participants that enrol in these studies need additional safeguarding to the conditions they are in [45,46]. Whereas uncertainties in risks-assessment have been addressed in the literature, this is much less the case for uncertainties regarding the benefits of research. We argue that identical to safeguarding participants from uncertainties in harm, we should safeguard FIH research participants from uncertainties in benefit, preventing them from enrolling in studies that are likely to be futile. In order to do this, we need a systematic way to assess the anticipated social value of the intervention tested. Here, we have provided some necessary steps for this assessment. It is important for researchers, RECs, funding agencies and the public at large to initiate a debate on social value. Moreover, as many before us have argued, transparency in clinical research is key.

References
1 Coller, B.S. and Califf, R.M. (2009) Traversing the valley of death: a guide to assessing prospects for translational success. *Sci. Transl. Med.* 1, 10
2 Castle, G. and Marshall, C. (2007) CHMP guideline on reducing risk in first-in-man trials: how will it affect your research? *EURALex* 20–22
3 European Medicine Agency (EMEA) (2007) *Guideline on Strategies to Identify and Mitigate Risks for First-in Human Clinical Trials With Investigational Medicinal Products.*
4 ABPI (2012) *Guidelines for Phase I Clinical Trials.*
5 U.S. Drug Administration (FDA) (2005) *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.* Washington, DC
6 Bernabe, R.D.C. *et al.* (2009) The need to explicate the ethical evaluation tools to avoid ethical inflation. *Am. J. Bioethics* 9, 56–58
7 Worp, B. *et al.* (2010) Can animal models of disease reliably inform human studies? *PLoS Med.* 7, e1000245
8 Emanuel, E.J. *et al.* (2000) What makes clinical research ethical? *JAMA J Am. Med. Assoc.* 283, 2701–2711
9 Habets, M.G.J.L. *et al.* (2014) The social value of clinical research. *BMC Med. Ethics* 15, 66
10 Barke, R. (2006) *Assessing Uncertain Risks and Benefits in Human Subjects Research.* 1–20
11 National Science Foundation (2008) *Science and Engineering Indicators 2008.* Washington
12 US Department of Health and Human Services. FDA (2004) *Innovation Stagnation. Challenge and Opportunity on the Critical Path to New Medical Products.*
13 Hay, M. *et al.* (2014) Clinical development success rates for investigational drugs. *Nat. Biotechnol.* 32, 40–51

14 Light, D.W. et al. (2013) Institutional corruption of pharmaceuticals and the myth of safe and effective drugs. J. Law Med. Ethics 14, 590–610

15 US Government Accountability Office (2015) DRUG SAFETY FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement. Washington, DC

16 Kimmelman, J. (2010) Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation. Cambridge University Press, Cambridge/New York

17 International Guidelines for Biomedical Research Involving Human Subjects. Council for International Organization of Medical Sciences (CIOMS)

18 Churchill, L.R. et al. (2003) Assessing benefits in clinical research: why diversity in benefit assessment can be risky. IRB: Ethics Hum. Res. 25, 1–8

19 McGonigle, P. and Ruggeri, B. (2014) Animal models of human disease: challenges in enabling translation. Biochem. Pharmacol. 87, 162–171

20 Kilkenny, C. et al. (2009) Survey of the quality of experimental design, statistical analysis and reporting of research using animals. PLoS ONE 4, e78

21 Webb, D.R. (2014) Animal models of human disease: inflammation. Biochem. Pharmacol. 87, 121–130

22 Sena, E. et al. (2007) How can we improve the pre-clinical development of drugs for stroke? Trends Neurosci. 30, 433–439

23 Kimmelman, J. and London, A.J. (2011) Predicting harms and benefits in translational trials: ethics, evidence, and uncertainty. PLoS Med. 8, e1001010

24 Hooijmans, C.R. and Ritskes-Hoitinga, M. (2013) Progress in using systematic reviews of animal studies to improve translational research. PLoS Med. 10, e1001482

25 Landis, S.C. et al. (2012) A call for transparent reporting to optimize the predictive value of preclinical research. Nature 490, 187–191

26 Macleod, M.R. et al. (2004) Pooling of animal experimental data reveals influence of study design and publication bias. Stroke 35, 1203–1208

27 Dyson, A. and Singer, M. (2009) Animal models of sepsis: why does preclinical efficacy fail to translate to the clinical setting? Crit. Care Med. 37, S30–S37

28 Begley, C.G. and Ellis, L.M. (2012) Drug development: raise standards for preclinical cancer research. Nature 483, 531–533

29 Genske, A. and Engel-Glatter, S. (2016) Rethinking risk assessment for emerging technology first-in-human trials. Med. Health Care Philos. 19, 125–139

30 Kimmelman, J. and Henderson, V. (2016) Assessing risk/benefit for trials using preclinical evidence: a proposal. J. Med. Ethics 42, 50–53

31 O'Collins, V.E. et al. (2006) 1,026 experimental treatments in acute stroke. Ann. Neurol. 59, 467–477

32 Chapman, A.R. (2011) Addressing the ethical challenges of first in-human trials. J. Clin. Res. Bioethics 2, 113

33 Linkov, I. et al. (2008) Nanotoxicology and nanomedicine: making hard decisions. Nanomedicine 4, 167–171

34 Buonsenso, D. et al. (2010) Management of central nervous system tuberculosis in children: light and shade. Eur. Rev. Med. Pharmacol. Sci. 14, 845–853

35 Science Media Centre (2016) Expert Reaction to French Drug Trial – Reports of One Patient Dying and Five Others in Hospital and of the Paris Prosecutor's Office Having Opened an Investigation into What Happened. http://www.sciencemediacentre.org

36 Li, G.L. et al. (2012) Assessment of the pharmacology and tolerability of PF-04457845, an irreversible inhibitor of fatty acid amide hydrolase-1, in healthy subjects. Br. J. Clin. Pharmacol. 73, 706–716

37 Huggins, J.P. (2012) An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. Pain 153, 1837–1846

38 Zarin, D.A. et al. (2007) Issues in the registration of clinical trials. JAMA 297, 2112–2120

39 Darren, B. et al. (2016) Sharing clinical trial data – a proposal from the International Committee of Medical Journal Editors – NEJM. N. Engl. J. Med. 374, 384–386

40 Czarnitzki, D. et al. (2014) Delay and secrecy: does industry sponsorship jeopardize disclosure of academic research? Ind. Corp. Change 24, 251–279

41 Lexchin, J. et al. (2003) Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 326, 1167–1170

42 Montaner, J.S. (2001) Industry-sponsored clinical research: a double-edged sword. Lancet 358, 1893–1895

43 Stretton, S. et al. (2016) Sponsor-imposed publication restrictions disclosed on ClinicalTrials.gov. Account. Res. 23, 67–73

44 Glass, J.D. et al. (2012) Lumbar intraspinal injection of neural stem cells in patients with amyotrophic lateral sclerosis: results of a phase I trial in 12 patients. Stem Cells 30, 1144–1151

45 Dresser, R. (2009) First-in-human trial participants: not a vulnerable population, but vulnerable nonetheless. J. Law Med. Ethics 37, 38

46 Dresser, R. (2016) First-in-human HIV-remission studies: reducing and justifying risk. J. Med. Ethics http://dx.doi.org/10.1136/medethics-2015-103115

Michelle G.J.L. Habets*
Johannes J.M. van Delden
Annelien L. Bredenoord

Department of Medical Humanities, Julius Center for Primary Care and Health Sciences, University Medical Center Utrecht, Heidelberglaan, 100, 3584 CX Utrecht, The Netherlands

*Corresponding author:

Features • PERSPECTIVE