Author’s response to reviews

Title: Combining value of information analysis and ethical argumentation in decisions on participation of vulnerable patients in clinical research

Authors:

Gert Jan van der Wilt (GertJan.vanderWilt@radboudumc.nl)
Janneke Grutters (Janneke.Grutters@radboudumc.nl)
Angela Maas (Angela.Maas@radboudumc.nl)
Herbert Rolden (Herbert.Rolden@gmail.com)

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Dear Editor,

Thank you for the reviews of our manuscript entitled "Excluding vulnerable patients form clinical research. The case of novel oral anticoagulants in premenopausal women with atrial fibrillation" (METH-D-17-00131). We feel that our manuscript has given rise to two important misunderstandings:

[1] We have by no means wished to suggest that women, generally, should be considered vulnerable. We have made the point that, much more specifically, premenopausal women using novel oral anticoagulant drugs for atrial fibrillation can be considered vulnerable, because of their increased risk of serious bleeding that are difficult to control. To avoid this misunderstanding, we have added (in italics):

[The current paper provides an example of the second class (risk-based vulnerability). It addresses the question whether premenopausal women with atrial fibrillation (AF) should participate in clinical studies of novel oral anticoagulants (NOACs).] By this, we do not wish to suggest that women, generally, should be considered vulnerable. In the context of the use of NOACs, however, premenopausal women can be considered vulnerable, as explained below.

[2] We have not intended to suggest that the method used in this paper, specifying norms, is a novel method. It was presented by Henry Richardson in his 1990 paper, and has been used in several contexts since that time (including, of course, in the work by Richardson himself). Also, it has been recognized by Beauchamp and Childress as an important means of bringing general principles to bear on concrete cases. To avoid this misunderstanding, we have added (in italics):
Specifying norms is an established method of moral argumentation [23]. [It has been used to address issues ranging from access to medicines [23], the management of serious incidental findings in brain imaging research when consent for disclosure is declined [24], to global development [25].]

In addition, we have added to the introduction the key dilemma as also described in the JAMA paper by Emanuel et al (2000):

The ethics of clinical research depends on the fulfillment of requirements that result from values such as respect for autonomy and welfare of research subjects, non-maleficence, and optimal use of scarce resources [1]. In concrete situations, such requirements can be mutually conflicting. For instance, subjects who are eligible based on the scientific objectives of a study, but who are at substantially higher risk of being harmed or experiencing more severe harm, should be excluded from participation on the basis of the risk-benefit requirement. If, however, the treatment under investigation is likely to be used in such patients, they should be included to learn how the treatment affects them, thereby enhancing the social value of the study [1; p. 2704]. The method of specifying norms has been developed as a means to resolve such conflicts in a transparent and systematic way [2; 3; 4]. According to this method, establishing what follows from abstract, general values in concrete situations requires specification of those values. Specification is an argumentative process, where general norms are qualified by “adding clauses indicating what, where, when, why, by what means, by whom, or to whom an action is to be, is not to be, or may be done” so as to arrive at a more concrete interpretation about how best to honor the commitment to the general norm [2; p 295]. Specifications are not fixed but not arbitrary either, and depend on the particular context of the case and the range of values that are taken into account [2]. When requirements do conflict, this does not result by necessity from the concerning values, but from the particular way these values were specified. The task, then, is to identify those values and to develop alternative or further specifications of those values that are plausible and acceptable, given the particularities of the case, the range of values that are taken into account, and the formal criteria of specification [2]. In this paper, the method of specifying norms will be applied to the issue of participation of vulnerable patients in clinical research.

In addition, the first reviewer challenges the idea that review boards should consider economic arguments. That is, should they consider whether the costs that are incurred by a proposed study are justified by anticipated benefits? We do think that, in the future, review boards might want to consider this aspect more than is currently the case. This aspect is also mentioned by Emanuel et al in their JAMA paper (2000; 283: 2701 – 2711), What makes clinical research ethical? They state: “There are two fundamental reasons why social, scientific, or clinical value should be an ethical requirement: responsible use of finite resources and avoidance of exploitation. Research resources are limited.” (p. 2703) To make this point more explicitly, we have added (in italics):

While the former is a formal model of moral argumentation, the latter provides a framework for incorporating the economic costs and benefits of conducting research aimed at reducing uncertainty. It can be considered as a means to inform the judgment whether a proposed clinical study represents social value, as defined by Emanuel et al [1].
Following the second reviewer’s suggestions, we have checked the text for English language and changed the title into Combining value of information analysis and ethical argumentation in decisions on participation of vulnerable patients in clinical research.

The first reviewer surmises that we are trying to justify a trial that we wish to conduct. This is not the case. The current debate in the Netherlands is, in fact, whether a national registry should be set up to monitor the nature and frequency of side-effects of NOACs. Our study was conducted in the context of a national program on ethical aspects of clinical research (as stated in the acknowledgments).

Finally, we have adjusted and updated the list of references.

We look forward to hearing your decision on the revised manuscript.

On behalf of all co-authors, yours sincerely,

Gert J van der Wilt, PhD