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Short Communication

An Improved Risks and Benefits Assessment Tool for Institutional Review Boards

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ABSTRACT

Ethical oversight is a critical requirement to conduct clinical research involving human participants and Institutional Review Board (IRB) and it is responsible to evaluate the ethical elements of a clinical research. However, there is no consensus on criteria for evaluating risks and benefits to human participants. Therefore, this article reviews the evaluation of risks and the potential benefits of a clinical trial using Multi-Attribute Utility Theory (MAUT) and suggests the incorporation of 5 levels of likelihood that risk event will occur for the standardisation of risk and benefit utility values.

Keywords: Risks and benefits assessment, bioethics

INTRODUCTION

Ethical oversight is a critical requirement in the conduct of clinical research involving human participants. Institutional Review Boards (IRBs) are responsible to evaluate the ethical elements of a clinical research and their assessment usually follows ethical guidelines outlined by the World Medical Association (WMA), Council for International Organizations of Medical Sciences (CIOMS) and World Health Organisation (WHO). Additionally, IRBs are also required to ensure clinical research is designed in compliance with the International Conference of Harmonisation (ICH)-Guideline for Good Clinical Practice (GCP). ICH-GCP compliance provides public assurance that the rights, safety and well-being of trial subjects are protected and clinical trial data is credible.

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Ethical and scientific reviews are firmly established in Malaysia. Thus far, 14 IRBs are listed in the National Medical Research Registry (NMRR) who are tasked with providing independent guidance, advice and decision on clinical research involving human subjects. IRBs in Malaysia follow international guidelines such as 'International Ethical Guidelines for Biomedical Research' (Vallotton, 2000), 'Operational Guidelines for Ethics Committees that Review Biomedical Research' (WHO, 2000) and 'Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants' (WHO, 2011), independently or together with local guidelines on the conduct of ethical and scientific reviews.

The most important oversight that an IRB is responsible for is risk and benefit assessment. Currently, there is no consensus on the criteria for evaluating risks and benefits of human participants. IRBs' evaluation is usually based on clinical judgement which is unavoidably subjective and intuitive (Van Luijin et al., 2006). For example, guideline 8 on page 195 of 'Benefits and risks of studying participation in the International Ethical Guidelines for Biomedical Research' (Vallotton, 2010) states:

> *'Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such 'beneficial' interventions or procedures must be justified in relation to expected benefits to the individual subject.'*

> *'Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.'*

Section 6.2.1.2 on page 10 of 'Scientific design and conduct of the study in Operational Guidelines for Ethics Committees that Review Biomedical Research' (WHO, 2000) describes that:

> *'The justification of predictable risks and inconveniences weighed against the anticipated benefits for the research participants and the concerned communities.'*

Standard 7 on page 13 of 'Ethical basis for decision-making in research ethics committees in Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants' (WHO, 2000) describes:

'In ethically acceptable research, risks have been minimized (both by preventing potential harms and minimizing their negative impacts should they occur) and are reasonable in relation to the potential benefits of the study. The nature of the risks may differ according to the type of research to be conducted. Research Ethics Committee (REC) members should be aware that risks may occur in different dimensions (e.g., physical, social, financial, or psychological), all of which require serious consideration. Further, harm may occur either at an individual level or at the family or population level.'

Such subjective statements are not very helpful when assessing risk-benefit because regulations and guidelines do not evidently describe "risks" and "benefits" nor do they define what determines risks acceptable (or reasonable or justified) in relation to expected benefits (Levine, 1988; Kimmelman, 2004; Rid et al., 2010; Rid & Wendler, 2011). Lack of regulations and guidelines in relation to risks and benefits may lead to inconsistent IRB decisions and a significant ethical and practical concern (Wendler et al. 2005; Rid et al. 2010; Rid & Wendler, 2012). The common concerns are: (i) some IRBs may provide inadequate protections for human subjects because they underrate risks, overemphasize expected benefits, or both; (ii) some IRBs may hinder valuable research because they overestimate risks, underestimate expected benefits, or both; and (iii) if a study involves multiple study sites, inconsistent IRB risk/benefit decisions at different sites could delay final approval without reason and waste resources (Silberman & Kahn, 2011; Klitzman, 2015). Hence, there is a need for tools which are both systematic and of use in strengthen in risk-benefit assessment. It is the aim of this article to review a model and suggest how its applicability maybe improved.

Recently, Bernabe et al. (2012) described the evaluation of risks and potential benefits of a clinical trial using Multi-Attribute Utility Theory (MAUT). MAUT is a decision theory that is basically "concerned with making trade-offs among different goals" and this is achieved by assigning utility values and weights to attributes of a study. Weight is multiplied with utility value for each attribute; the product of all attributes are added together and that total value will provide a global picture or summary for risks and benefits for the trial (Baron, 2008). Utility value is generally defined as a numerical representation of human goals that have been determined by a decision maker while weight is usually the influence of each utility in a trial (Bernabe et al., 2012).

Each trial has a total weightage of 1 which is distributed among the risk attributes of the trial. Bernabe et al. (2012) assigned same weight of 0.5 to both individual experimental intervention risks and trial participation risks due to their comparable importance (Table 1). Experimental intervention risks usually refer to potential

harms caused by the investigational drugs or trial procedures whereby trial participation risks typically refer to potential discomforts or burdens encountered when participating in a trial. The authors further divided the weight for the experimental intervention risks equally between the comparator and trial drug arms, i.e., 0.25 each. Weight for the trial participation risk is similarly distributed equally between certain harms and risks due to trial participation. Each sub-category in the experimental intervention risks and trial participation risks was assigned a negative utility value that is determined either by the IRBs, investigators or sponsors based upon their moral beliefs, intuitions, empirical data or experiences (Bernabe et al., 2012).

Table 1
Multi-Attribute Utility Theory used to evaluate the risks of a clinical trial

Risks due to experimental intervention (side effects) (0.5*)		Risks due to trial participation (0.5*)	
Comparator arm (0.25*)	Trial drug arm (0.25*)	Certain harm due to trial participation (0.25*)	Risks due to trial participation (0.25*)
-3**	-4**	-4**	-3**

*weight
**utility value

In Table 2, they assigned a weight of 0.5 each to two benefit attributes; benefits to participants and benefits to society, due to equal importance of these benefits. Benefits to participants were further categorised into direct benefits and inclusion benefits, and assigned weight of 0.4 and 0.1, respectively. Direct benefits are those that can be expected from the trial interventions. Inclusion benefits also known as collateral or indirect benefits are benefits obtain in a trial regardless of whether the participant receives the experimental intervention or not. Additionally, each sub-category under direct benefits was assigned a weight of 0.2 each while another 2 sub-categories under inclusion benefits were assigned weight of 0.05 each. Utility values for benefits are assigned positive integers.

Table 2
Multi-Attribute Utility Theory used to evaluate the benefits of a clinical trial

Benefits to participants (0.5*)				Benefits to society (0.5*)
Direct benefits (0.4*)		Inclusion benefits (0.1*)		
Comparator Arm (0.2*)	Trial Arm (0.2*)	Certain Inclusion benefit (0.05*)	Probable Inclusion benefit (0.05*)	
3**	3**	3**	3**	8**

*weight
**utility value

Risk-benefit index was then decided based on the sum of products of weight and utility value for each of the sub-categories for both risks and benefits as shown in Tables 1 and 2. Their calculation for the risk attribute was (0.25) x (-3) + (0.25) x (-4) + (0.25) x (-4) + (0.25) x (-3) = -3.5, whereas the benefit attribute was (0.2) x (3) + (0.2) x (3) + (0.05) x (3) + (0.05) x (3) + (0.5)(8) = 5.5. The addition of these two values yielded a positive index of 2 [(-3.5) + (5.5)] indicating that the benefits outweigh risks. If the index had been a negative, it will mean that risks outweigh benefits.

METHODOLOGY

Standardisation of Risks and Benefits Utility Value

Bernabe et al. (2012) reported MAUT is an easy ethical assessment tool that could provide a more balanced and rationally defensible decision. The MAUT is a "summary measure of how consequences realise ultimate values or good" (Baron, 2008). However, there is still an element of subjectivity in the determination of utility value of risks and benefits evaluation. Without some sort of standardisation, there may be much variation between determinations of each IRB resulting in different risk-benefit assessment for the same trial. We, thus, propose standard guide for determining utility value for risk based on a Risk Management Guide (US DoD, 2006) in Table 3. The risk utility value is based on 5 levels of likelihood that risk event will occur. Similarly, we developed a benefit utility value table based, too, on the likelihood of occurrence of the benefit (Table 4). We further re-categorised "risks due to trial participation" into "certain harm" and "collateral risk" as it is felt that the original sub-categories may be confusing. We define "certain harm" as harm from the study procedures, such as blood taking, biopsies, and other invasive procedures. "Collateral risk" is defined as mental, economic or social risk that may potentially be associated with trial participation, such as worries that one is on placebo and social stigma associated with the study disease.

Table 3
Utility value of likelihood risk event will happen

Utility Function (u)	-1	-2	-3	-4	-5
Likelihood	Remote	Unlikely	Likely	High Likely	Near Certainty

Table 4
Utility value of likelihood benefit event will happen

Utility Function (u)	1	2	3	4	5
Likelihood	Remote	Unlikely	Likely	High Likely	Near Certainty

The proposed utility value determinations are next utilised in risk-benefit assessment of a mock trial. The mock trial is to evaluate the effectiveness of a newly discovered beta-blocker drug to control hypertension. This new drug is believed to have similar pharmacodynamics with current top selling beta-blocker but potentially costs much less. Weights used by Bernabe et al. (2012) were retained for risk attributes (Table 5). Utility values for risks due to the experimental intervention were assigned value of -3 as both comparator and trial arms have similar side effects and are likely to occur. Next, for risks due to trial participation, a utility value of -3 was assigned to certain harm as serious adverse events for all study procedures are unlikely to happen. A utility value of -1 was assigned to collateral risk as this type of risk is remote for the type of study investigational product and medical condition.

Table 5
Multi-Attribute Utility Theory to evaluate the risks of a mock trial

Risks due to experimental intervention (0.5*)		Risks due to trial participation (0.5*)	
Comparator arm (0.25*)	Trial drug arm (0.25*)	Certain harm (0.25*)	Collateral risk (0.25*)
-3**	-3**	-3**	-1**
(0.25x-3)+(0.25x-3)+(0.25x-2)+(0.25x-1) = -2.25			

*weight
**utility value

Consequently, benefit assessment was scored (Table 6). Similar to risk, weights for the benefit attributes used by Bernabe et al. (2012) were retained. Utility values for direct benefits of comparator and trial arms were assigned with 5 to represent the near certainty that both drugs will lower the blood pressure of participant. Trial participants

were given free drugs and monitored closely, more than usual, by trial team and thus the sub-category 'certain inclusion benefit' was assigned a utility value of 5. However, the sub-category 'probable inclusion benefit' was only assigned a utility value of 1 because participants in both intervention arms receive the same standard management, the only difference being the drug given. Additionally, category 'benefits to society' is assigned utility value of 3 as the experimental drug is likely to be a cheaper alternate to current anti-hypertensive drugs.

Table 6
Multi-Attribute Utility Theory to evaluate the benefits of a mock trial

Benefits to participants (0.5*)				Benefits to society (0.5*)
Direct benefits (0.4*)		Inclusion benefits (0.1*)		
Comparator Arm (0.2*)	Trial Arm (0.2*)	Certain Inclusion benefit (0.05*)	Probable Inclusion benefit (0.05*)	
5**	5**	5**	1**	3**
(0.2x5)+(0.2x5)+(0.05x5)+(0.05x1)+(0.5x3) = 3.8				

*weight
**utility value

RESULTS AND DISCUSSION

The sum of the product of weight and utility value for risk was -2.5 and for benefit was 3.8. Adding these 2 sums together gave a risk-benefit index of 1.3. Thus, the benefit of this trial outweighs its risk. By incorporating the 5 levels of likelihood with MAUT, we had successfully presented the standardisation for the utility value for risks and benefits that are systematic and can be utilised to strengthen risk-benefit assessment.

CONCLUSION

With the addition of the guide for determination of utility values for risk and benefit, MAUT is an advantageous tool for risk-benefit assessment with the standardisation of the parameters used for risk-benefit assessment because it is an easy ethical assessment tool that will provide a more balanced and rationally defensible decision making. Although, there are various quantitative risks and benefits methodologies as reported by International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Risk-Benefit Management Working Group (Guo et al., 2010), we found that all these assessment tools are specific to assess drug safety and efficacy. Thus, MAUT could be the more suitable tool that can be adapted by IRB to assess the ratio between risks and benefits of various types of clinical research including drug trials, procedures, devices and observational studies.

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