Introduction

The Safety Monitoring Board (SMB) is concerned with clinical endpoints of mortality or major morbidity. A clinical study within U-BIOPRED may be of an observational nature, or may evaluate a treatment intervention for which the safety record is not established. Vulnerable patient populations, such as infants or the elderly, may be studied. The independent nature of the SMB is critically important to its mission, as it allows all organizations involved in clinical study management to continue in their functions without the presence or perception of bias. The SMB will act in a decisive capacity throughout U-BIOPRED to monitor patient safety, decide on safety issues, coordinate crisis management, evaluate the efficacy of the intervention and provide input to EMA. The decisive capacity means that the steps decided on will be given directly to and need to be followed by the (local) study leaders.

Mission Statement

The SMB will work in a collegiate, collaborative and inclusive manner according to the human equivalence principle to provide safety guidance and balanced opinion in order to enhance the excellence U-BIOPRED aspires to. The SMB will elevate the awareness of and disseminate information on safety issues.

Terms of Reference

The initial responsibility of the SMB will be to protect the safety of the study participants by monitoring and acting on the safety issues of (clinical) studies within U-BIOPRED. Therefore, the SMB responsibilities are to:

- set standards (patient safety and related parameters) according to which the patient safety of clinical trials will be evaluated (so-called standard operating procedure or SOP for the SMB). Criteria include participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site (regarding safety issues), and other factors that can affect safety aspects of the study. Procedures will be discussed at the first SMB plenary or teleconference meeting;

- review the research protocol and amendments regarding safety and monitoring issues/requirements according to the SOP for the SMB, and recommend applicable modifications. The recommended modifications are compulsory. The SMB will do additional reviewing until the documentation is regarded sufficient;

- evaluate the progress of the (clinical) studies regarding safety issues according to the SOP for the SMB at least every year as well as recommend or decide on adaptations to the protocol or study execution;

- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the study participants. If external factors are relevant to the safety, the SMB will decide on study adaptation;
review clinical centre performance at least every 6 months, make recommendations and assist in the resolution of safety problems reported by the respective work package leaders and/or responsible scientists;

decide, independent of the Scientific or Management Board, which steps need to be taken concerning continuation, termination or other modifications of the study arms based on the observed beneficial or adverse effects in the study. Modifications may include inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in study procedures, adjustments in sample size, changes in duration of observation and follow up, and report issues to the independent IMI safety committee. The steps decided on by the SMB need to be followed. If the decisions are not being followed, the SMB has the capacity to put the study on hold until the issue has been resolved. Study hold should occur to prevent safety risks foreseen without implementation of SMB recommendations;

conduct, if appropriate, if appointed to and upfront described in the protocol/amendment, an interim analysis of efficacy in accordance with stopping rules which are clearly defined in advance of data analysis and have the approval of the SMB;

coordinate the safety crisis management in case of a safety crisis during the execution phase of a clinical trial or study in collaboration with the respective work package leaders, trial investigators and Management Board. Crisis management and consequent measures to be taken will primarily be done by the local study management in accordance with legal and regulatory authority requirements. The SMB will act and decide on the overall project level by evaluating and estimating the effects and consequences of the locally arising safety issues and subsequent locally taken decisions for the project as a whole. The procedure is described in the SMB-SOP on crisis management;

by a members’ only distribution list. Communication with the wider U-BIOPRED community will be via common e-mail distribution list and via the U-BIOPRED website.

each individual clinical site will have to report any events to the clinical research organisation (CRO) and to U-BIOPRED.

The reporting on SAEs to the local ethics committees will be done by the CRO or by the Investigators accordingly to the applicable regulation in force. The CRO will inform all other clinical sites about reportable* events. The CRO also informs the U-BIOPRED Ethics Board, Safety Monitoring Board and Management Board as well as WP3 management. The SMB monitors annually that the CRO is doing this and use the information in their annual U-BIOPRED safety reports;

evaluate its own performance annually. Criteria include time (for responding and finalizing issues), quality and adequacy of response;

assist U-BIOPRED in collecting all safety data and information needed by EMA where applicable using the SMB files;

ensure the confidentiality of the study data and the results of monitoring given to the SMB for the reason of data evaluation. All materials and discussions of the SMB are contribute towards a project safety and governance policy and advise on, and where appropriate contribute to, the safety training of project partners.

maintain communication between SMB members completely confidential. Members and other participants in SMB meetings are expected to maintain
confidentiality. Confidentiality issues and meeting formats will be dealt with in the SOP for the SMB. Summaries of the meetings, and annual as well as the final U-BIOPRED report of the SMB are available for wider disclosure via the U-BIOPRED website taking into account the good scientific conduct and ethics criteria as described in the SOPs for both the U-BIOPRED Ethics Board and the SMB. In contrast to legal safety and data monitoring boards the U-BIOPRED SMB will not deliver safety reports as this will be dealt with by the CRO;

- provide public statements, oral and written presentations on behalf of the SMB where it should be presumed that public statements regarding SMB activities are made in the spirit of corporate representation. Such statements must be clearly distinguished from any statements made in a personal capacity.

Membership
The steering committee of Work Package 10 shall be responsible for establishing the Safety Monitoring Board, as well as for appointing the members of the Safety Monitoring Board. The Safety Monitoring Board will be independent from the Management Board. The board consists of 7 members (chair inclusive): 1 member from patient organizations, 2 clinical scientists, one paediatrician, a (clinical) pharmacologist, a safety advisor, a biostatistician, and will be chaired by the scientific WP10 leader or chosen by the WP10 chairs from within the Safety Monitoring Board. Apart from the patient members and chair, the membership consists of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Written documentation attesting to absence of conflict of interest is required. A list of members of the U-BIOPRED SMB is given in appendix B.

*: reportable events: the CRO will file a copy of all types of SAEs and send scanned versions of the SAEs to the chair of the U-BIOPRED SMB. The unexpected and related SAEs are protected by coding.
In order to evaluate (clinical) study protocols or designs with human beings or their derived biomaterials and to monitor such ongoing studies from the perspective of patient safety, the following criteria are set:

1. Technical and methodological aspects:
   - quality and robustness of study design, methodology (incl. statistics), number(s) of participants, and medical technical assessment;
   - availability, level of suitability and accurate use of rescue medication;
   - accurateness of experimental and clinical procedures including brief descriptions on e.g. re-use of disposable medical devices, and quality and safety of medicines;

2. Experience and adverse events:
   - level of experience or skills of researcher(s) related to the methods to be used;
   - risk level of and ability to deal with (serious and severe) adverse events including hospital acquired infections;
   - incidence of all adverse events and study discontinuations

3. Monitoring of study progress:
   - progress of patient inclusion,
   - approval and approval duration by legal ethics committees, and
   - study progress as a whole.

Your comments to each of the 3 paragraphs:
Please provide both positive and negative aspects

1. Technical and methodological aspects
2. Experience and adverse events
3. Monitoring of study progress (unless this is described in the protocol, this will be part of the monitoring process)

Your decision and advice to the project leaders:

Endorse without comment : yes / no
Modify according to your comments : yes / no
Reject (comments compulsory) : yes / no

Your name:

Date:
Patient’s Perspective Criteria List
Criteria for evaluation of research protocols, study designs and other documents from the patient’s perspective

1. **Relevance.**

1.1 health related quality of life
   (improvement of quality of life: physically, mentally and socially)
1.2 Improvement of health
   (improvement of health of patient group)
1.3 Applicable to more diseases
   (takes into account patients suffering from multiple diseases (co-morbidity) and complications)
1.4 Improvement of care for patients
   (leads to improved care for patient group)
1.5 Improvement of societal participation
   (improved participation in and being part of the society)
1.6 Exploitable result
   (project result can be used in practice and associates with characteristics of patient group e.g. age, ethnicity, social economic status)
1.7 Applicability of project result in practice
   (a plan is available how to bring the results into practice)

2. **Right of Say.**

2.1 Patients are a source of knowledge
   (this deals with wishes, needs and sores of the patient group and acknowledges the value of disease experiences)
2.2 Patients are equal discussion partners
   (the patient group also decides on a research project, proposal, protocol, guideline or policy)
2.3 Patients are full citizens
   (the image of the patient group as being independent and self-thinking citizens with a chronic disease or disability)

3. **Ethics and Safety.**

3.1 The method is the least aggravating in relation to the goal
   (this is the least burdening way reaching the goal – there is no less burdening alternative for the patient group)
3.2 Safety of participants in the study
   (side effects, discomfort, aftermath, and after care are being taken care of by the project, and this is known to participants)
3.3 Freedom of Choice
   (participant signs in full freedom to participate in the study or not without reduction in the quality of basic health care provision)
3.4 Rules, codes, social norms and values
   (the project adheres to behavioural codes, professional codes and legal medical regulations and laws regarding research with humans)
3.5 Human dignity
   (the project leaders regard participants in a holistic way and do not regard the disease only)
3.6 Responsibility and Carefulness
   (the project leaders informs the own physician about the project if the participant approves to this. Participants know the complaint procedure)
3.7 Information about the project results
   (project results will be fed back to participants and the patient group in lay terms i.e. in terms that can be understood by 95% of the national population)
Total scores of:

1. relevance (max. 70 points)
2. right of say (max. 30 points)
3. ethics and safety (max. 70 points)

To each aspect 10 points (highest and best appreciated) can be given maximally.
Neutral score of 5 points: aspect is not described and should not be described in the protocol.
Score 0 – 5 points: aspect is not described, but should be described in the protocol.
Protocol must be improved!
Score 5 – 10 points: aspect is described in the protocol.

Your comments to each of the 3 paragraphs:
Please provide both positive and negative aspects

1. Relevance

2. Right of Say

3. Ethics and Safety

Your advice to the project leaders:
Endorse without comment: yes / no
Modify according to your comments: yes / no

Your name:
Date:

# criteria based on:
Clarification of the criteria.

Relevance

1.1 **health related quality of life**
   The expected project results improve the quality of life of the patient group (physically, mentally or socially). Less physical limitations during daily activities caused by health-related problems like climbing stairs, body washing, clothing and shopping. Less mental limitations due to feelings of anxiety or depression. Less social limitations due to the way the disease affects the possibilities to act in a family, participate at work or spare time activities, or to visit family or friends.

1.2 **Improvement of health**
   This is important for improvement of health of the patient group.

1.3 **Applicable to more diseases**
   The description pays attention to comorbidities and/or complications, is there any relevance to other diseases. There is no need for unnecessary replication in other diseases.

1.4 **Improvement of care for patients**
   The expected project result leads indeed to an improved health care as experienced by patients.

1.5 **Improvement of societal participation**
   Improved possibilities to participate in the society: e.g. being volunteer at school or elsewhere, being member of a society, or being employed.

1.6 **Expansible result**
   The expected project results are utilisable for the patient group.

1.7 **Applicability of project result in practice**
   The project plan also contains an implementation plan how results can be brought into practice – if not then the patient group will not profit.

Right to say

2.1 **Patients are a source of knowledge**
   The project is also based on wishes and needs of the patient group. Acknowledgement of the value of patient’s disease experiences is given next to professional knowledge.

2.2 **Patients are equal discussion partners**
   The patient group is one of the parties in the project, and involved in e.g. negotiations on study design, study execution, evaluation, dissemination and implementation. The project information is available in lay terms and understandable by 95% of the population. Feedback of the project results will also be done in lay terms.

2.3 **Patients are full citizens**
   Within the project patients are being regarded as full, self-conscious and emancipated citizens, and are not being regarded as unemancipated and dependent citizens.

Ethics and Safety

3.1 **The method is the least aggravating in relation to the goal**
   If the project result seems relevant for other diseases then the project leaders should inform the research and care field about this (principle of universality). Are the benefits from the project higher than the burden (e.g. a better drug for asthma versus patients undergoing an intervention to see whether the drug makes them better or sicker). What is the risk of failing to work, go to school or participate in social activities? This is the only way to reach the goals. There are no alternatives less burdening for patients available based on the informed consent.

3.2 **Safety of participants in the study**
   In case of patient-bound research the project leaders take care of providing a suitable insurance for participants related to disease burden, failure to work, study or participate in social activities. Side effects, discomfort, aftermath, and after care are being taken care of by the project, and this is known to participants.

3.3 **Freedom of Choice**
   Participants will be provided (written) information in lay terms about the project, and more than 24h to think about their participation. The information is given as a patient informed consent form, which includes the freedom to make their own choice to participate (yes or no). It should be stated explicitly that their choice will not affect the quality of health care provided by their caregivers. Participants will also get written information on the complaint procedure.
3.4 **Rules, codes, social norms and values**
The project leaders have follow the legal (local and national) regulations and laws, and rules regarding behavioural and professional codes.

3.5 **Human dignity**
The project leaders have a holistic view about the participants – hence they not only view the patient part but also an individual with a family, friends, education or being employed, and with spare time. The project leaders avoid that participants feel helpless or ashamed.

3.6 **Responsibility and Carefulness**
The project leaders and scientists take care of the participants in the best possible way. The project leaders should provide information to the patient’s physician about participation and potential consequences of the research (i.e. side effects, discomfort etc.).

3.7 **Information about the project results**
Project results should be provided to the patient group and participants in lay terms.