Avenue E. Mounier 83/11
1200 Brussels
Belgium
Tel: +32 2 774 1611
Email: eortc@eortc.be
www.eortc.org

Permanent Independent Data Monitoring Committee (IDMC) for EORTC studies
IDMC Charter

Version: 1.0
Effective on: 16 NOV 2015

Authorised by:
Name: Malcolm MASON
Role: IDMC Chairman
Signature:
Date: 24.11.15

Prepared by
Name: Laurence COLLETTE
Role: Head of IDMC Support Unit
Signature:
Date: 24.11.15

• CONTENT	CHARTER DETAILS
• **1. Introduction**	
Outline of scope of charter	This document describes the purpose and roles of the members of the permanent IDMC for EORTC. It describes the qualifications and responsibilities of each committee member. The IDMC (IDMC = Independent Data Monitoring Committee) shall be formed for each study according to the terms specified in EORTC POLICY 004 by adjunction of study specific independent experts to the permanent IDMC.
• **2. Roles and responsibilities**	
A broad statement of the aims of the committee	To safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.
Terms of reference	The IDMC should receive and review information on the progress and accumulating data of this trial and provide advice on the conduct of the trial. The IDMC should make recommendations to the Study Management Group and the Study Steering Committee regarding the following aspects of the study; as is relevant in regard to the study design: ♦ whether it is ethical to continue randomizing patients when there is compelling evidence that the risk/benefit ratio favors one of the arms over the other(s) or conversely, where there is compelling evidence of futility (i.e., that the study will never lead to concluding against the null hypothesis) following protocol defined stopping rules. ♦ whether one should present or publish the results of all or some of the study endpoints earlier than anticipated, i.e., prior to study maturity ♦ whether a randomized phase II study should be continued (or possibly expanded) into a phase III study. ♦ whether a modification should be made to the study for safety reasons, for example, a modification of the eligibility criteria when the risk/benefit ratio seems unfavorable in specific subgroups of patients ♦ on early termination of a trial when the scientific value of the trial is insufficient, either because of compelling external evidence regarding the hypothesis being tested or because the trial will not be able to produce scientifically valid results due to lack of accrual or lack of quality ♦ on modifications to the study sample size ♦ on study parameters that are planned according to an adaptive study design when the adaptions are effects based on an interim analysis of un-blinded results of the controlled study (generally involving comparative analyses of study endpoints or outcomes potentially correlated with these endpoints). ♦ on actions needed to manage identified issues related to patient compliance or study feasibility and/or quality
Specific roles of IDMC	Interim review of the study's progress including adherence to protocol treatment and follow-up, and main outcomes and safety data. Specifically, these roles include to:

• **CONTENT**	**CHARTER DETAILS**
	• monitor evidence for treatment harm (e.g. toxicity, SAEs and SARs, deaths) • assess the impact and relevance of external evidence • decide whether to recommend that the study continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups • decide whether study follow-up should be stopped earlier • maintain confidentiality of all study information that is not in the public domain • consider the ethical implications of any recommendations made by the IDMC • monitor planned sample size assumptions, preferably with regards to (i) a priori assumptions about the control arm outcome and/or (ii) emerging differences in clinically relevant subgroups, rather than on emerging, un-blinded differences between treatment groups, overall[1] • suggest additional data analyses if necessary • advise on protocol modifications proposed by investigators or sponsors (e.g. to inclusion criteria, study endpoints, or sample size) • monitor compliance with previous IDMC recommendations
• **3. Before or early in the study**	
Whether the IDMC will have input into the protocol	All potential study-specific IDMC members should have sight of the protocol before agreeing to join the committee. However it is not planned that IDMC members would have input in the study protocol before its start. Before recruitment begins the study will have undergone review by the EORTC Protocol Review Committee, scrutiny by other study committees and ethical committees and/or other regulatory bodies. Therefore, if a potential study-specific IDMC member has major reservations about the study (e.g. the protocol or the logistics) they should report these to the EORTC IDMC Chair and may decide not to accept the invitation to join. IDMC members should be independent[2] and constructively critical of the ongoing study, but also supportive of aims and methods of the study.
Whether the IDMC will meet before the start of the study	The IDMC reviews the study according to the schedule specified in the study protocol or at the request of the Study Management Group after its start. The IDMC does not review the study protocol before it is approved by the EORTC Protocol Review Committee
Any issues specific to the disease under study	These are detailed in the study protocol

[1] It is advised that the sample size is not revised on the basis of the treatment effect at an interim analysis. This is because the type I error and power would have to be recalculated on the basis of the correlation between the observed estimate of the treatment effect and the final target estimate. This problem is analogous to the interim looks at the accumulating data but is, perhaps, more difficult to assess because we are conditioning on the future.

[2] Independence will result from the joint expertise of the members of the IDMC. Is to be seen as absence of conflict of interest, direct or indirect, financial or scientific, for the study for which data monitoring is required. Therefore NO pharmaceutical company representatives may be members of the IDMC or attend its closed or confidential meeting sessions.

• **CONTENT**	**CHARTER DETAILS**
Any specific regulatory issues	The EORTC studies are covered by the EU Clinical Trials Directive and will be co-ordinated accordingly. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf). All EORTC studies also comply with the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation. SUSARs/SARs/SAEs will be reviewed and reported in the appropriate manner before being compiled in the IDMC report.
Any other issues specific to the treatment under study	These are detailed in the study protocol
Whether members of the IDMC will have a contract	IDMC members will not formally sign a contract but should formally register their assent to join the group by confirming (1) that they agree to be on the IDMC and (2) that they agree with the contents of this Charter by signing the last page of the document.
• **4. Composition**	
Membership and size of the IDMC	The IDMC for each study is composed according to the rules specified in EORTC Policy 004 "Independent Data Monitoring Committees for EORTC studies. It thus includes all permanent members of the IDMC in place at the time of each review of the study and external independent experts appointed by the IDMC Chair for each study Permanent and study-specific IDMC members shall not be permanent members of other EORTC review committees such as the EORTC Protocol Review Committee or the EORTC Scientific Audit Committee, they shall not have entered patients themselves or have been responsible for treatment of patients in the study being reviewed, nor shall they have any official function within the study (e.g. they should not be member of any drafting committee or other independent committee involved in the conduct or endpoint assessment of the study). Likewise they may not be an officer of the EORTC Group responsible for the study at the time of the review. They should also not be the principal investigator of any competing study. Members who previously acted as external (occasional) reviewers (e.g. for EORTC Protocol Review Committee) for the study being reviewed should declare this as potential conflict of interest. Members shall not have been on advisory boards either (a) for the same drug as the study drug, or (b) for the same Pharma company AND the same indication as in the study, if not the same drug. Members who have been on advisory boards for the same company as the one involved in the study (if any), but for a different drug and a different indication should declare this but would not be excluded. If a permanent member has to be replaced for the review of a given study because of conflict of interest, the other IDMC members will identify and approve an appropriate replacement.

• CONTENT	CHARTER DETAILS
	Such replacements will be documented in the minutes of the IDMC meetings and a note to the IDMC study file will indicate that "for this study, the following permanent member • name of permanent member was replaced by … • name of replacement of permanent member for any meetings that occurred during the term of name of permanent member on the EORTC IDMC"
The Chair, how they are chosen and the Chair's role. (Likewise, if relevant, the vice-Chairman)	The IDMC Chair will have previous experience of serving on IDMCs, experience of Chairing meetings and will be able to facilitate and summarize discussions. The Chair will be nominated and agreed by the EORTC Board for an initial term of 3 years which is renewable at the discretion of the EORTC Board. The Chair is expected to facilitate and summarize discussions. A vice-Chair will not be appointed. Should the IDMC Chair need to be replaced for the review of a specific study due to conflicting interests or other reasons; or should he/she need to be replaced for a whole meeting, the most senior member of the IDMC (the one who has longest term on the IDMC) will usually be selected to Chair the IDMC as replacement. Such an event will be documented in the minutes of the IDMC.
The responsibilities of the IDMC statistician	The IDMC membership will include a statistician to provide independent statistical expertise, especially with regard to interpretation of accumulating data and guidance through the report. The IDMC statistician will not prepare the IDMC reports.
The responsibilities of the (un-blinded) study statistician	For open-label trials, the study statistician will have overall responsibility for the production of the report to the IDMC and will participate in IDMC meetings, guiding the IDMC through the report, participating in IDMC discussions and, on some occasions, taking notes. For blinded studies, the un-blinded statistician will take the role of the study statistician during the IDMC.
The responsibilities of the (un-blinded) EORTC Headquarters study team	For open-label trials, the EORTC Headquarters study team will help the trial statistician to produce the report to the IDMC. The Clinical Research Physician and the EORTC statistician may attend open and non-restricted closed session of the IDMC meeting; other members of the Study Management Group may only attend the open sessions. If the trial is blind, the un-blinded CRP (pharmacovigilance physician) and the un-blinded statistician substitute for the EORTC Headquarters team in the preparation of the IDMC report and in attending the confidential session of the IDMC meeting.
The responsibilities of the Study Coordinator(s)	The Study coordinator(s), as well as other members of the Study Management Group should be invited and should be available, to attend open sessions of the IDMC meeting. The Group Chair or Study Specific Committee members or representatives from industry financially supporting the study will not usually be expected to attend but may be invited to join the open sessions when necessary (See Organisation of IDMC Meetings).
• **5. Relationships**	
Relationships with study	The responsibilities of each study committee are detailed in the

• CONTENT	CHARTER DETAILS
coordinators, Study Management Group(SMG)[3], other study committees (e.g. Study Steering Committee (SSC)[4], sponsor and regulatory bodies)	protocol. The relationships between these groups are displayed in **Figure 1.**
Clarification of whether the IDMC is advisory (make recommendations) or executive (make decisions)	The IDMC is advisory to the Study Steering Committee and Study Management Group. Both the Study Management Group (SMG) and the IDMC make comments, requests and recommendations to the SSC.
Payments to IDMC members	IDMC members will receive no financial remuneration for their time. Travel expenses encountered by IDMC members, the Study Coordinator and HQ members will be reimbursed by the EORTC treasury. For fully supported studies, operating and administrative expenses will also be charged in the contract with the pharmaceutical company. No other payments or rewards are given.
The need for IDMC members to disclose information about any competing interests	Competing interests should be disclosed (using the EORTC Confidentiality Agreement and Interest Disclosure Form (EORTC QS-002-AF-03). These are not restricted to financial matters – involvement in other studies or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. IDMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
• **6. Organisation of meetings**	
Expected frequency of IDMC meetings	The IDMC meets four times a year, approximately every three months. At each meeting, the IDMC will review only the studies that are scheduled for an interim analysis according to their protocol; or those for which the Study Management Group identified emergent issues for which the IDMC advice is sought. The wishes of the IDMC and needs of the studies will be considered when planning each meeting.
Whether meetings will be face-to-face or by teleconference	The first meeting after the appointment of a new IDMC Chair will generally be face-to-face. To facilitate full discussion and ensure a good functioning of the committee, face-to-face meetings are preferred, with video-supported teleconference (Webex) as a second option. It is recommended that at least

[3] **Study Management Group (SMG):** For an EORTC study the study management group consists of the EORTC Headquarters core team in charge of running the study (clinical research physician, statistician, project manager and data mangers) and the principal study coordinator

[4] **Study Steering committee (SSC) (also named Study Executive Committee, or Study Executive Board**): the Study Steering Committee (SSC) is the committee that provides the overall supervision of the study and has executive power . The SSC should monitor study progress and conduct and give advice on scientific credibility. The SSC will consider and act, as appropriate, upon the recommendations of the IDMC. Membership of the SSC shall, as a minimum, include the study coordinators, the representatives of collaborative groups involved, as third parties and at least one representative of the EORTC Headquarters and the representative of the Sponsor. When EORTC is the sponsor, the EORTC study clinical research physician is the representative of EORTC as sponsor For some protocols, the SSC may sometimes be named differently, for example the Study Executive Committee, or Study Executive Board. When no SSC has been formally set up for an EORTC study, SSC in this study will then refer to the Study Coordinators (principal and co-coordinators) and the Chairperson of the EORTC groups involved in the study, and there will be at least one member of the EORTC HQ team (usually the EORTC study Clinical Research Physician) in charge of the study at the EORTC Headquarters plus the representative of the study sponsor

• CONTENT	CHARTER DETAILS
	one meeting should be face-to-face each year. Review by email exchanges only is not normally recommended but it may be permitted in exceptional circumstances with the agreement of the IDMC Chair
How IDMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	A mixture of open and closed sessions will be held. Only permanent IDMC members and external IDMC experts they specifically invite are present in the restricted closed sessions. In open sessions, all those attending the closed session may be joined by representatives of Study Management Group and sometimes also representatives of the sponsor, funder, or regulator, as relevant. The format of the IDMC meetings will be based on the following structure: Every meeting of the IDMC starts with a restricted business session: the IDMC discusses running business issues together in a closed session with the EORTC IDMC Support unit staff. Then, for each trial to be reviewed at the meeting, the following structure follows: 1. Optional IDMC-only closed session: IDMC members may wish to discuss the study to be reviewed together before discussing with the Study Management Group. 2. Open session: discussion of open parts of report with the Study Management Group 3. Confidential session: The un-blinded statistician presents the confidential report to the IDMC. The un-blinded clinical research physician may attend the session to answer questions of the IDMC. (For Open label studies, the study statistician and study clinical research physician attend the session). 4. IDMC-only closed session: The IDMC discusses the study results and develops its recommendations, which are drafted during the session. Only the IDMC members attend. The IDMC support Unit staff (may attend if invited by the IDMC Chair, to take minutes. The recommendation letters are finalized and approved within 5 business days of the IDMC meeting. All IDMC members review and agree the contents of the letters of recommendations. The IDMC Chair approves and signs the final version.
• 7. Study documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in <u>open</u> sessions	Accumulating information relating to recruitment and data documentation (e.g. data return rates, treatment compliance, safety reporting) will be presented. Toxicity details based on pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may also be presented, at the discretion of the IDMC.
Intended content of material to be available in <u>confidential</u> sessions	In addition to all the material available in the open session, the confidential session material will include safety analyses broken down by treatment group and results of efficacy analyses broken down by treatment group if stopping rules are planned by the design. The un-blinded results are disclosed during the confidential session only.
Whether or not the IDMC will be blinded to the treatment allocation	The IDMC will not be blinded to treatment allocation.
The people who will see the	The accumulating data and interim analysis by randomised group

• CONTENT	CHARTER DETAILS
accumulating data and interim analysis	will be seen by the IDMC members and the statistician and clinical research physician who prepared the report. These results are also seen by members of the EORTC IDMC Unit who review and approve the reports and/or distribute them. This information is not made available to anybody else outside the IDMC and EORTC IDMC Support Unit staff. IDMC members and EORTC Staff do **not** have the right to share confidential information with anyone outside the IDMC.
Responsibility for identifying and circulating external evidence (e.g. from other studies/ systematic reviews)	Identification and circulation of external evidence (e.g. from other studies/ systematic reviews) is not the responsibility of the IDMC members. The Study Management Group will collate any such information for presentation in an open session.
To whom the IDMC will communicate the decisions/ recommendations that are reached	The IDMC reports its recommendations in writing to Study Management Group who forwards it to the Study Steering Committee and other relevant parties (supporting bodies, collaborative groups... In its communications, the IDMC should be careful not to relay any confidential information to the SSC, study coordinator or blind study team. The IDMC should take care to maintain the blinded status of the study coordinator with regard to interim study data.
Whether reports to the IDMC be available before the meeting or only at/during the meeting	The IDMC should receive the report at least 2 weeks and preferably at least 4 weeks before any meetings.
What will happen to the confidential papers after the meeting	The IDMC members should confidentially store the papers after each meeting. After the study is reported, the IDMC members should destroy all interim reports. A copy of all of the reports will be held at EORTC IDMC Support Unit. Fresh copies of previous reports may be circulated (by email) with the newest report before each meeting. Confidential documents are password protected. Passwords are sent separately.
• **8. Decision making**	
What decisions/recommendations will be open to the IDMC	Possible recommendations from the IDMC include:- • No action needed, study continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment, clear lack of benefit or external evidence. In this case, the interim results are generally made available to the SSC. • Stopping recruitment within a subgroup (care should be taken if this is not a pre-specified subgroup). In this case, the interim results are generally made available to the SSC. Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up duration Stopping a single arm of a multi-arm trial • Proposing or commenting on proposed protocol changes • Commenting on proposed Statistical Analysis Plan or changes to the study design Changes proposed and/or approved by the IDMC may require protocol amendments and thus submission and approval by the EORTC Protocol Review Committee. In such instance, the Headquarters study team should make the IDMC recommendation letter available to the Protocol Review Committee upon

• CONTENT	CHARTER DETAILS
	submission of the amendment.
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	Formal statistical methods are more generally used as "stopping" guidelines rather than absolute rules. This is because they generally only consider one dimension of the study. Reasons should be recorded for disregarding a stopping guideline. The statistical guidelines for the study are described in the study protocol and explained further in the introduction sections of the interim analysis report.
How decisions or recommendations will be reached within the IDMC	The Chair is to summarise discussions and encourage consensus; it is usually best for the Chair to give their own opinion last. Every effort should be made for the IDMC to reach a unanimous decision. If the IDMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the recommendation letter as these may inappropriately convey information about the state of the study data. It is important that the implications (e.g. ethical, statistical, practical, financial or else) for the study be considered before any recommendation is made. The EORTC IDMC Support Unit Staff have no voting right in this process.
When the IDMC is quorate for decision-making	Efforts should be made to ensure that all IDMC members can attend the meeting. The EORTC IDMC secretary will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference or videoconference. If, at short notice, any IDMC members cannot attend at all then the IDMC may still meet if at least two thirds of the permanent IDMC members will be present, including the Chair or acting chair. If the IDMC is considering recommending major action such as stopping a trial or releasing results after such a meeting the IDMC Chair should call a meeting (by teleconference) with the full IDMC, including the absent members as soon as possible after the meeting to verify that the IDMC agrees with the recommendation.
Can IDMC members who cannot attend the meeting input	As the report is circulated before the meeting, IDMC members who will not be able to attend the meeting in person or by teleconference are expected to pass written comments to the IDMC Chair via the EORTC IDMC Support Unit for consideration during the discussions.
What happens to members who do not attend meetings	If an IDMC member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend the following meeting, they should be asked if they wish to remain part of the IDMC. If a member does not attend a third meeting, they should be replaced.
Whether different weight will be given to different endpoints (e.g. safety/efficacy)	The primary trial endpoint is given the strongest weight in the assessment of the benefits to the patients. All safety aspects have prime importance to the assessment of the risk to patients entering the study.
• **9. Reporting**	
To whom will the IDMC report their recommendations/decisions, and in what form	This will be through a recommendation letter sent to Study Management Group (with a copy to the EORTC Group Chair), usually within 5 working days of the meeting (see Section 7). A copy of this will be stored at EORTC IDMC Support Unit.
Whether minutes of the meeting be made and, if so, by whom and	Minutes of the meeting will be prepared by the head of the IDMC Support Unit, unless the study is blind. If the study is blind, then

• CONTENT	CHARTER DETAILS
where they will be kept	the IDMC Chair or another designated IDMC member will take the minutes. The minutes are reviewed and approved by all members and signed by the IDMC Chair.
What will be done if there is disagreement between the IDMC and the body to which it reports	The final decision to act on the recommendations is the responsibility of the Study Steering Committee (SSC) represented by the Study Coordinator. The IDMC would generally expect that its recommendations would be endorsed by the SSC unless there is an exceptional reason to do otherwise. If the Study Steering Committee disagrees with the recommendations of the IDMC, the Study Steering Committee should formulate a reply to the IDMC, sent by the study coordinator within 4 weeks of receipt of the IDMC recommendations which should fully justify their reasons not to follow the recommendations. A copy of this letter must be sent to all members of the Steering Study Committee. The matter will be debated between the IDMC and the Study Steering Committee in a dedicated meeting. The head of the IDMC Support Unit also attends the meeting. The information to be shown would depend upon the action proposed and the IDMC's concerns. Confidential data would generally not be divulged during such meetings as it is likely to influence the further conduct and further publications of the trial and would be detrimental to the scientific merit of the trial In the event that an agreement cannot be reached, the case will be escalated to the General Director and the Chairman of EORTC who will make a final decision. Depending on the reason for the disagreement confidential data would often have to be revealed to them confidentially for informing their final decision.
• **10. After the study**	
Publication of results	The IDMC may wish to see a written undertaking that the trial results will be published in a correct and timely manner. Depending on the results of the study and the ease of their interpretation, the IDMC may wish to see the final data and give advice about data interpretation and publication. If they so wish, this will be specified in the recommendation letter
The information about the IDMC that will be included in published study reports	IDMC members will not be named in the study publications. A brief summary of the timings and conclusions of IDMC meetings should be included in the body of this paper.
Whether the IDMC will have the opportunity to approve publications, especially with respect to reporting of any IDMC recommendation regarding termination of a study	The IDMC may wish to be given the opportunity to read and comment on any publications before submission. If so wished, the IDMC will clearly stipulate this demand in their recommendation letter.
Any constraints on IDMC members divulging information about their deliberations after the study has been published	The IDMC members should not discuss issues relating to their involvement in the study at any time, and the content of IDMC meetings will remain confidential.

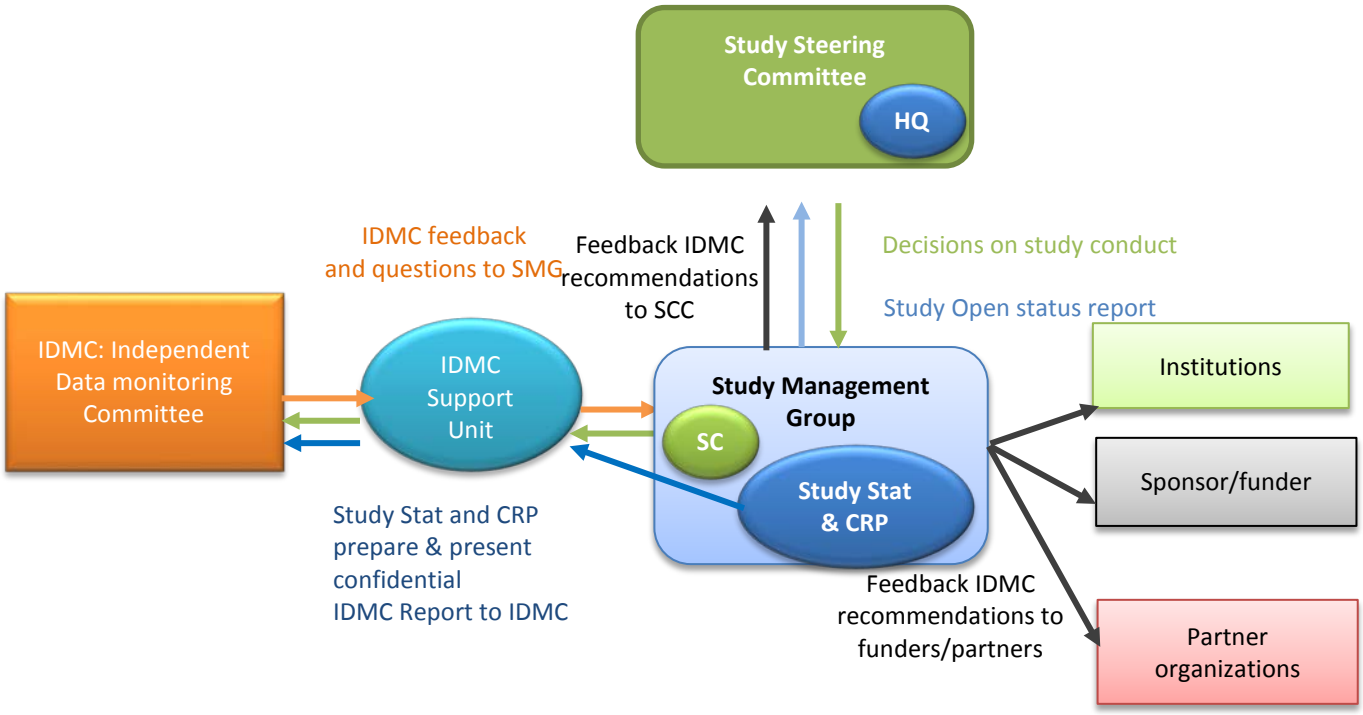
Signature for IDMC members

I the undersigned accept to take part in IDMC meetings as an expert. I agree to the terms and conditions led out in

this Charter and I do hereby undertake to apply them and be bound by them		
Name & affiliation	Role on IDMC: *(select)*	• Permanent member • Study-specific member
Signature:	Date:	

Figure 1:

a) For open-label trials



b) for blind trials