Canadian Cancer Trials Group (CCTG)

Policies for the Data Safety Monitoring Committee

V002 January 8, 2013
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1 Policy

The Canadian Cancer Trials Group (CCTG) will have a single Data Safety Monitoring Committee (DSMC) that is advisory to the Director of the CCTG. Every clinical trial conducted by the CCTG must include a plan for data and safety monitoring as part of the protocol:

1. All phase III trials led by the CCTG will include oversight by the DSMC.

2. Phase II trials meeting the following criteria will include oversight by the DSMC:
   - Single arm trials with a sample size of 100 patients or more
   - Randomized trials with sample size of 80 patients or more
   - Trials that include blinded therapy

3. Intergroup trials in which the CCTG participates, but are led by another cooperative group, are expected to include a DSMC. In the unusual circumstance in which another cooperative group conducts a trial that is not overseen by a DSMC, negotiations to consider a role of the CCTG DSMC may be considered.

4. Trials of the IND Program that do not meet criteria for DSMC review will be reviewed by a process that is internal to that Program (SOP: TMG-SOP-0158). For IND trials not meeting criteria for DSMC review and should unique trial-related issues exist, the IND Program may request DSMC review.

Among the parameters satisfied by the procedures of the DSMC of the CCTG for monitoring Phase III trials is ensuring that these procedures are in accordance with the National Cancer Institute, United States (NCI US) Cooperative Group Data Monitoring Committee.

2 Introduction and Scope

The importance and complexity of safely and rigorously conducting randomized controlled trials necessitates the need for independent Data and Safety Monitoring Committees. The concept for these committees, known by a variety of names that account for their roles and membership, was first developed in the 1960s\(^1\) and since that time, considerable literature about their purpose, function and accountability has been generated\(^2-5\). In general, accepted broad mandates include ensuring that the safety of patients / subjects enrolled onto trials is protected, that integrity of trial data and analysis is preserved given the potential importance of trial results to future patients, and that trial feasibility issues are appropriately monitored given the scarcity of research funding and the opportunity cost involved with every trial\(^2-5\). The purpose of this document is to provide a description of the DSMC of the CCTG, including its scope, accountability, and operational components.

This document has taken into account principles gleaned from DSMC literature, including a comprehensive document developed by the Data Monitoring Committees: Lessons, Ethics and Statistics Study Group (DAMOCLES)\(^2,5\). The document also recognizes Health Canada’s principles and requirements of International Conference on Harmonization Good Clinical Practice guidelines\(^6\), and recognizes the contributing and leadership roles played by the CCTG in the
conduct of trials supported by the NCI (US) and the need to comply with DSMC requirements of the NCI US\textsuperscript{7,8} and Cancer Therapy Evaluation Program (CTEP)\textsuperscript{9}. Requirements for DSMCs developed by the NCI US have been applied across cancer cooperative groups in the United States; associated information from some of these groups has been used to help develop this document\textsuperscript{10-12}.

The broad responsibilities of the DSMC of the CCTG are to assist in protecting the safety of trial participants and to facilitate meeting the mission of the CCTG which is “to develop and conduct clinical trials aimed at improving the treatment and prevention of cancer with the ultimate goal of reducing morbidity and mortality from this disease”. In order to meet this mission, the DSMC must assist in ensuring that the results of trials are valid and credible and that the continued conduct of a given trial will be consistent with this mission.

3 Definitions

3.1 Terms

Data Safety Monitoring Committee

The CCTG will have a single DSMC that is advisory to the Director, and responsible for assessing, at intervals, the progress of a clinical trial, safety data, and critical efficacy endpoints, and to recommend to the Director whether to continue, modify, or stop a trial. The DSMC will be comprised of individuals who are both members and non-members of the CCTG; these individuals will be independent from those CCTG members responsible for carrying out the trials under consideration, including the faculty and staff of the CCTG Central Office.

Clinical Trials Committee

The Clinical Trials Committee (CTC) is responsible for advising the Director on all substantial issues related to the scientific agenda of CCTG including its policies and clinical trials. The CTC is responsible for approving and prioritizing the initiation of individual trials. In this capacity, the CTC may be responsible for receiving the written DSMC summary minutes and deliberating on the recommendations of the DSMC and advising the Director about the implications of these recommendations for the CCTG.

Central Office Safety Processes

The CCTG has standard processes for ongoing evaluation of safety. These are outlined in a series of Standard Operating Procedures and Work Instructions. These processes are designed to ensure the safety experience on trials is reviewed regularly by comparing the experience to what was expected, reviewing adverse event reporting and availability of a new safety information (e.g. Investigator Brochures) and ensuring information that should go to patients, investigators, Research Ethics Boards (REBs) and regulatory authorities is provided. This internal review process includes oversight by the Safety Desk of the Compliance and Oversight Office and the Trial Team.

Study Chair and Trial Committee

The Study Chair of a CCTG trial is the CCTG member, external to the Central Office, who is responsible for leading the trial. The Trial Committee includes the Study Chair, co-investigators external to the Central Office of the CCTG chosen to assist in leading the trial, and members of the CCTG Central Office responsible for leading the trial including the Physician Coordinator, Statistician and Study Coordinator. The names and roles of these individuals are recorded on the face sheet of every trial protocol.
3.2 Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>CCTG</td>
<td>Canadian Cancer Trials Group</td>
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<tr>
<td>CTC</td>
<td>Clinical Trials Committee</td>
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<td>CTEP</td>
<td>Cancer Therapy Evaluation Program</td>
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<td>CTSU</td>
<td>Clinical Trials Support Unit</td>
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<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
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<td>ERG</td>
<td>Ethics and Regulatory Affairs Group</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>NCI US</td>
<td>National Cancer Institute (United States)</td>
</tr>
<tr>
<td>REB</td>
<td>Research Ethics Board</td>
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</tbody>
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4 Terms of Reference

4.1 Accountabilities

The responsibilities of the DSMC are to advise the CCTG on all matters related to the safety of subjects enrolled in its trials, and on selected matters related to the integrity and potential conclusions of study data and the appropriateness of continued trial conduct. The DSMC is advisory to the Director of the CCTG. The recommendations of the DSMC and resulting actions will be communicated throughout the CCTG, including to the CTC, Disease Site Chairs, IND Program, Trial Study Chairs and Committees and membership. Where the Director and the Chair of the DSMC disagree, a specific presentation of a given item by the Chair of the DSMC to the CTC can be arranged (either at a CTC meeting or through a conference call).

For trials involving NCI US and CTEP, the recommendations of the DSMC and CCTG responses to these recommendations will be communicated to these agencies and additionally distributed according to NCI US and CTEP policies. As the DSMC is advisory to the Director of the CCTG, in the unlikely situation where the Director does not concur with the DSMC, specific communication by the CCTG Director with the CTEP Associate Director is required. The Chair of the DSMC will be included in discussions with the Director and the CTEP Associate Director.

For trials not involving NCI US and CTEP for which the Director and the DSMC disagree, the Director, in conjunction with the Chair of the DSMC will convene an ad hoc committee of 1-3 CTC members who have no potential conflict of interest with the item in question, in order to review the issue and provide additional advice to the Director.

For trials in which the CCTG Director has direct scientific involvement, (i.e., is the Physician Coordinator), the DSMC will make its recommendations to the CCTG Deputy Director. Identical processes will then ensue with the Deputy Director assuming those Director roles described above.

The recommendations of the DSMC and the CCTG responses to these recommendations will be available for local REBs of centers participating in CCTG trials, and where applicable, to industry and other regulatory collaborators.

4.2 Scope by Trial Type

4.2.1 Phase III Trials

All phase III trials led by the CCTG will include oversight by the DSMC.
4.2.2 Phase II trials

Phase II trials meeting the following criteria will include oversight by the DSMC:

- Single arm trials with a sample size of 100 patients or more
- Randomized trials with sample size of 80 patients or more
- Trials that include blinded therapy

Trials of the IND Program that do not meet criteria for DSMC review will be reviewed by a process that is internal to that Program (SOP: TMG-SOP-0158). For IND trials not meeting criteria for DSMC review and should unique trial-related issues exist, the IND Program may request DSMC review.

4.2.3 Intergroup Trials

The terms of reference and composition of the DSMC are set to meet requirements of the NCI US. The DSMC of the CCTG is responsible for all trials led by the CCTG, including intergroup trials led by the CCTG. Intergroup trials in which the CCTG participates, but are led by another cooperative group, are expected to include a DSMC. In this case, the responsibility for DSMC oversight is with the lead group responsible for the trial. In the unusual circumstance in which another cooperative group conducts a trial that is not overseen by a DSMC, negotiations to consider a role of the CCTG DSMC may be considered.

When the CCTG is the coordinating group of a NCI US sponsored intergroup trial, a CTEP representative must be included as a DSMC member for these trials. As the DSMC is advisory to the Director of the CCTG, as indicated in section 4.1.1, in the unusual situation where the Director of the CCTG does not agree with the advice of the DSMC, a specific consultation process between the Director and the CTEP Associate Director is required. The DSMC Chair will be included in such discussions.

4.2.4 Investigational New Drug Program (IND) Trials

Phase II trials conducted within the IND Program that meet criteria described in 4.2.2 will include DSMC oversight. Phase I trials and Phase II that do not meet criteria described in 4.2.2 will be reviewed by a process that is internal to the IND Program and will not be included in the mandate of the DSMC. These processes are detailed in SOP: TMG-SOP-0158. The IND Program may request DSMC oversight for IND trials that are not otherwise mandated to have DSMC review should these trials include specific issues that the IND Program deems would benefit from independent review.

4.3 Responsibilities within Trials Oversight

4.3.1 Safety of Trial Participants

The DSMC is responsible for reviewing safety and adverse event data. Sources of data for review include adverse event tables as are normally provided in CCTG Meeting Books, including specific updating for each DSMC conference, minutes from monthly CCTG Central Office safety procedures, and where applicable pharmaceutical company and regulatory agency communications. These materials for review will be collated and / or prepared for the DSMC by the Central Office in accordance with its Standard Operating Procedures. Where necessary, the DSMC will make recommendations for corrective action which may include early termination, suspension or modification of a trial, or changes in consent processes.

4.3.2 Integrity of the Trial Data and Conclusions

The DSMC will review all planned interim analyses, major proposed amendments that affect trial outcome measures or accrual targets, and any requests for unplanned analyses or release of trial
results prior to the protocol – defined primary analysis. The DSMC will advise whether, and to whom, outcome results should be released if analyses are performed prior to the protocol – defined primary analysis.

4.3.3 Trial Feasibility and Relevancy

As part of their review of CCTG trials, the DSMC will regularly assess the accrual rates to all studies to ensure that their completion remains feasible. Where this is judged not to be the case, the committee will recommend closure to the Director of the CCTG. As a broad guideline, the DSMC may apply the criteria developed by NCI US and CTEP which state that closure of trials should be recommended if the accrual rate of the trial during the fifth to sixth annual quarter following trial activation is less than 20% of the projected accrual for that quarter. Similarly, if the accrual rate during the fifth to sixth quarter is greater than 20% but less than 50% of projected, the DSMC may recommend that specific measures to improve accrual or alter study design be provided.

New data from studies external to the CCTG might influence the design, safety or relevance of a CCTG trial. The Study Chair of the Trial Committee of a CCTG trial will be asked to provide the results of such studies to the DSMC. The DSMC may recommend continuing, amending or closing a study based on such new evidence.

4.3.4 Duration of Oversight

Trials will continue to be reviewed by the DSMC until the trial is closed to accrual and analysis of the primary outcome completed. For trials that are closed to accrual where all patients have completed protocol therapy and analysis of the primary outcome is pending, the DSMC will only be required to review late toxicity tables.

5 Membership

5.1 Chair of the DSMC

The DSMC is chaired by a member of the CCTG who is external to the Central Office. Appointment of the DSMC Chair is the responsibility of the CCTG Director, taking into account advisement of the CTC. Prior DSMC experience is a criterion used in selecting the Chair. The Chair is expected to provide leadership on administrative and scientific issues, have medical and trial methodology expertise and be able to facilitate discussion, integrate differing points of view and ensure that processes to reach consensus are implemented.

The term of appointment for the DSMC Chair is 3 years, renewable once.

5.2 DSMC Membership

Members of the DSMC will include members of the CCTG who are external to the CCTG Central Office and individuals who are not members of the CCTG. Members are identified and selected through a consultative process that includes the Chair of the DSMC and the Director of the CCTG. For logistical reasons, the DSMC is kept small, while maintaining representation of all required skill areas and experience. Membership of the DSMC will include 9 – 14 individuals that ensure representation on the DSMC of the individuals with expertise or representation of the following categories:

i) systemic therapy of cancer (at least 2)
ii) radiation oncology (at least 2)
iii) surgical oncology (at least 1)
iv) biostatistics (at least 1)
v) clinical trials methodology (at least 1)
vi) ethics (at least 1)
 vii) lay representative (at least 1)
viii) NCI US / CTEP representative (1)
ix) Non NCI US / CTEP cooperative group member external to CCTG (1) All of these members will be voting members of the DSMC.

Members of the DSMC may have roles, including that of Study Chair, of studies monitored by the DSMC. In such situations, the DSMC member should indicate a conflict of interest and be absent when any discussions or voting of that specific trial are conducted.

The terms of appointment for the DSMC members are normally 3 years, renewable once. In special circumstances of unique needs, and after a consultation process between the Chair of the DSMC and the Director of the CCTG, a member may be requested to participate for a longer term. Members may be appointed on an ad hoc basis through a consultation process involving the DSMC Chair and the Director of the CCTG should additional expertise be required in the review of certain studies.

5.3 CCTG Central Office Membership on the DSMC

The DSMC will include a designated CCTG Central Office research staff individual who will be a non-voting member, and responsible for providing administrative assistance to the DSMC.

5.4 Compensation, Confidentiality and Conflict of Interest

5.4.1 Compensation

No payment or rewards will be given to DSMC members for their participation on the committee. Members of the DSMC will be reimbursed according to CCTG Group Policy for travel costs and hotel accommodations.

5.4.2 Confidentiality

No communication of the deliberations or recommendations of the DSMC, either written or oral, should be made outside of the Committee except as indicated in section 6.4. Knowledge of interim data and analyses is restricted to members of the DSMC during the course of a trial, including any follow-up period, until the trial is completed and the results are released. This information should be securely protected from inadvertent or inappropriate access to non-DSMC members.

As per CCTG Group Policy, a “Statement of Confidentiality” must be provided by all DSMC members before each DSMC meeting. Members of the DSMC will have confidential access to a DSMC file on the CCTG website. Access to this website includes confidentiality policies that pertain to all DSMC materials.

5.4.3 Conflict of Interest

Conflicts of interest deserve special consideration with respect to DSMC activities. The CCTG Group Policy on conflicts of interest related to potential financial activities will apply to the DSMC. Individuals with a potential conflict of interest should inform the Chair of the DSMC to determine whether the individual should be absent during any discussions or voting on specific trial issues.
Members of the DSMC may also be investigators who have a participating role on specific trials and may therefore also have a potential conflict of interest; for instance, their knowledge of interim results could influence their conduct during the trial. Members that may have such a conflict should inform the DSMC Chair to determine whether the individual should be absent during any discussions or voting on specific trial issues.

The CCTG Director will review possible conflicts of interest and determine whether there is sufficient basis to exclude the individual from serving on the DSMC.

6 Meetings

6.1 Schedule and Scope

The CCTG DSMC will review all Phase III trials at six month intervals. At least one of these meetings will be face-to-face, generally at the CCTG Spring Meeting. The second may be in the form of a conference call held in the Fall. In addition, ad hoc teleconferences may be necessary in some situations, particularly when new information must be urgently considered (i.e. to review planned interim analysis data or review emerging safety data).

All trials within the purview of the DSMC will be reviewed at each meeting. It is expected that the context of this review will always include assessment of safety (as per section 4.3.1) and accrual (as per section 4.3.3). Additional aspects for review will include interim analyses; the study protocol will generally describe the schedule and statistical approach to the interim analysis of trial data. Also, the Study Chair / Trial Committee may communicate specific requests for analyses or provide external data for review.

All DSMC members are expected to be familiar with materials provided for each trial for each meeting. The DSMC Chair will delegate responsibility for leading the discussion of each trial under review to specific DSMC members so that this leadership role is shared appropriately.

6.2 Materials

At the time of the Spring Meeting, the DSMC is provided with:

i) A copy of the DSMC’s internal minutes from its most recent previous meeting
ii) A list of trials to be reviewed at that meeting
iii) An DSMC Trial Abstract provided by the CCTG Trial Committee
iv) The CCTG Meeting Book Tables: This web-based document includes a one-page trial summary and trial schema, accrual and eligibility data, baseline characteristics of entered patients, toxicity data, and in selected instances, reporting of other outcome data
v) Additional SAS Meeting Book Tables for all open and closed blinded trials. Event data are presented by 'masked' treatment arm. The treatment arm will not be identified unless required by the DSMC.
vi) All relevant correspondence related to Central Office safety procedures
vii) Any additional information provided by the CCTG Central Office (e.g., additional safety data, communications from pharmaceutical companies or regulatory agencies).
viii) Any trial – specific communications from the Study Chair or Trial Committee.
ix) Any data requested by the DSMC as a result of their previous meeting(s).
x) In the instance where an interim analysis is to be assessed, the DSMC will receive a report from the trial statistician that provides the background to the trial, the parameters of the interim analysis, and the results of this analysis. This responsibility of the trial statistician will include preparing all analyses, including interim analyses, of trials where treatment received is blinded and preparation of unblinded results is required.

At the time of the Fall Meeting, the DSMC is provided with identical material. These materials will be collated and / or prepared for the DSMC according to CCTG Standing Operating Procedures.

After meetings, DSMC members should shred any paper copies and delete from personal computers and / or electronic memory apparatus’ all DSMC meeting materials. The CCTG designated staff member responsible to the DSMC will ensure web-based materials are properly coded and maintained according to the CCTG document management procedures..

6.3 Meeting Format

The meeting will be divided into an open and a closed session, as determined by the DSMC Chair. Presence of a majority (50% + 1) of the DSMC voting members will constitute a quorum.

6.3.1 Open Session

When required, the DSMC will review trial material in an open session that includes participation, as invited guests to the meeting, of members of a Trial Committee. The DSMC may request presentations from a Trial Committee member (e.g., Trial Statistician, Study Chair, Physician Coordinator) regarding presentation of an interim analysis, or other specific issues such as accrual, consideration of new external data etc. It is optimal that the Trial Statistician be present at the open session of the DSMC when an interim analysis is to be reviewed. When any analysis involving blinded data is presented, no guests other than the trial statistician may be present at the meeting. Guests may be present for the open session for only the agenda items that deal with their specific trial.

6.3.2 Closed Session

The closed session will be restricted to DSMC members. Each trial will be reviewed with respect to relevant topics. The DSMC will attempt to reach a unanimous consensus with respect to the recommendations required for each trial. In circumstances where unanimous consensus cannot be reached, a vote will be taken with a resulting recommendation based on a majority of voting members present. The DSMC minutes will reflect the numbers voting for and against a given issue. No further details about the vote should be included in the minutes.

6.4 Recommendations

The responsibility of the DSMC is to make recommendations regarding the continuation of a study (with or without major or minor modifications), temporary suspension of enrolment and/or study intervention, or study closure and / or release of trial outcome information.

Recommendations and any additional commentary deemed appropriate by the DSMC will be communicated in writing to the Director of the CCTG. When the DSMC recommends a substantive alteration of trial conduct (e.g., study closure, release of trial results prior to a planned final analysis), the documents evaluated by the DSMC in their decision – making process will be made available to the Director. Any clarifications required will be considered by the Director of the CCTG in conjunction with the Chair of the DSMC.

Following the above clarification process, the DSMC Chair will complete a “DSMC Recommendation Report”. This report will include only the recommendations of the DSMC. The recommendations of the DSMC will be reviewed by the CTC. When necessary, direct
presentations by the Chair of the DSMC to the CTC will be arranged. This review process will, where appropriate, respect and maintain the confidentiality of the material reviewed by the DSMC, and the decisions resulting from evaluation of this material. Following review with the CTC, the Director will append to the DSMC Recommendation Report a response to each DSMC item indicating the nature of any required action.

For trials in which the CCTG Director has direct scientific involvement, (i.e., is the Senior Investigator), the DSMC will make its recommendations to the CCTG Deputy Director. Identical processes will then ensue with the Deputy Director assuming those Director roles described above.

The resulting document that includes DSMC recommendations and CCTG resulting actions will be referred to as the “DSMC Summary Report” and will be posted on the CCTG website for CCTG members and communicated to relevant stakeholders including intergroup collaborators, NCI US and CTEP, and will be available for investigators to circulate to their local REBs. For CCTG led trials that are on the Clinical Trial Support Unit (CTSU) menu, the CTSU is sent an excerpt of the DSMC Summary Report regarding those trials for posting to their members’ website. For CCTG trials that include collaboration with an industry partner, the DSMC Summary Report related to that trial will be forwarded to the partner.

When necessary, the Central Office staff member responsible to the DSMC will assist with administrative matters related to preparing these documents.

7 Records

Detailed minutes of all DSMC meetings are written by the DSMC Chair and reviewed by the Central Office staff member responsible to the DSMC. Once finalized, these minutes are posted to the DSMC private web page where they may be accessed by members of the committee. The Chair of the DSMC and Central Office staff member responsible to the DSMC must ensure that these minutes are consistent with the recommendations recorded in the DSMC Summary Report (described in section 6.4). The reason for any discrepancy between the detailed DSMC minutes and the DSMC Summary Report should be described in an annotation provided by the DSMC Chair.

8 Roles and Responsibilities

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<th>Responsibility</th>
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<tr>
<td>DSMC</td>
<td>• Responsibilities per CTG-POL-0005 to oversee data safety as described.</td>
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<tr>
<td>DSMC Chair</td>
<td>• External Chair appointed by CCTG Director.</td>
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<tr>
<td></td>
<td>• Provide leadership on administrative and scientific issues, provide medical and trial methodological expertise, and facilitate discussion.</td>
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9 Appendix

None.
10 References


11 Revision History

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<th>Version Date</th>
<th>Brief Description of Revision(s)</th>
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<td>V001</td>
<td>November 28, 2006</td>
<td>Initial Release</td>
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<tr>
<td>V002</td>
<td>January 8, 2013</td>
<td>Full review. Update to address Safety Conference Committee and to harmonize with TMG-SOP-0158 Safety Monitoring for IND Program Trials.</td>
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12 Signature

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<th>Signature of Responsible Group Leader:</th>
<th>Dr. Ralph Meyer</th>
<th>On File</th>
<th>January 14, 2013</th>
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<tbody>
<tr>
<td>Name</td>
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