Guidance Regarding Duration of Clinical Trials Used as Reference Support in Advertising

November 2023 (revised)

For healthcare products that do not have Terms of Market Authorization (TMA) limitations on duration, the following may be considered as reference support for advertising messages provided they meet all of the requirements in this advisory:

- Out-of-label studies evaluating a duration of use that is longer than the product's pivotal trials for the corresponding condition
- Published, pre-planned extensions and subsequent interim and final analyses of randomized, controlled trials (RCTs)

1. The study is consistent with the TMA

Clinical trials used as reference support in advertising should be consistent with the TMA of the promoted product as per s. 3.1 of the PAAB Code. When assessing consistency with the TMA, the PAAB considers:

i) Indication
ii) Patient population
iii) Limitations and directions for handling/use
iv) Dosing or use regimen/administration
v) Magnitude and direction of effect/risk

Limitations in duration of therapy identified in the TMA, such as might be stated in the dosing and administration section of the TMA, must be reflected in the out-of-label study in order for it to be accepted as reference support for advertising claims.

> Example: The TMA states that the product is given for 18 cycles. Out-of-label studies examining more than 18 cycles of treatment will not be acceptable as reference support for advertising claims.

1.a Pre-planned out-of-TMA updates **to TMA studies** that aren't fully consistent with TMA attributes i-iv:

With increasing frequency, the TMA includes studies whose protocols call for continued data collection/analysis for some specified time into the future (e.g., for a later interim analysis, an extension, or a long-term follow-up). These updates to TMA studies may be included in healthcare professional advertising provided all of the following criteria are met:

- they are pre-planned
- they are published and peer-reviewed
- they do not pertain to NOC/c products or class B opioid products

Inconsistencies between the study and the TMA with respect to attributes i-iv do not preclude the APS from featuring claims supported by the updated analysis provided:

- those are the same discrepancies as in the original study that was accepted into

the TMA
- the presentation is limited to the combination of endpoints and populations/subgroups featured in the TMA in relation to that study

Note that for "special studies" and other studies in the TMA that are not included among the pivotal trials, the study presentation in the APS must reflect the context, emphasis, and tone of the TMA.

IMPORTANT: Separate non-TMA studies (and/or their corresponding extension/follow-up analysis) may not appear in APS if they are inconsistent with the TMA. The fact that a study featuring one or more characteristics that are inconsistent with the TMA was accepted into the TMA does not support promotion of separate studies with similar issues/features.

1.b Pre-planned out-of-TMA studies and out-of-TMA updates to TMA studies conveying results that differ materially from the corresponding TMA results (TMA attribute 'v' above)

The APS must not selectively emphasize findings that convey materially different results from the TMA (with regards to either magnitude of effect/risk or direction/inference). When an APS presentation features study findings that materially differ from corresponding TMA study results, the TMA study results must be presented with similar prominence in the APS. This applies whether the new findings relate to a continuation of the TMA study (e.g., demonstrating attainment of statistical significance as the data matured at later pre-planned timepoints), or to an entirely separate study evaluating a similar endpoint and population as TMA study. In fact, when the new findings relate to a continuation of the TMA study, the updated findings should follow prominent presentation of the corresponding TMA findings from the earlier study timepoint. For example, the TMA indicates there was no statistical significance for an endpoint at year 3 of a study. Should an out-of-TMA update of the same study find that statistical significance was obtained at year 4, the year 3 finding should be conveyed prominently prior to (or at the same time as) the year 4 finding. Marketing claims of benefit are permissible provided no attribute of the study or presentation triggers the need for a claim-neutral (i.e., informational) presentation.

2. The study meets standards for high quality evidence

Clinical trials must meet all requirements for evidence outlined in the PAAB Code and PAAB guidelines.

For a list of some of the key relevant resources & guidances CLICK HERE.

Published, pre-planned extensions or subsequent interim/final analyses that do not meet all

requirements for evidence in the PAAB Code and PAAB guidelines may also be acceptable as reference support in advertising provided that:

- The original RCT meets PAAB Code requirements for evidence.
- The presented endpoints from the extension/subsequent analysis are endpoints that were acceptable from the original RCT
- Content relating to and findings from the extension/subsequent analysis are presented separately from and following the presentation of relevant findings from the original RCT as a secondary presentation
- Findings from the extension/subsequent analysis are presented in a claim-neutral (i.e., informational) manner with no claims

2.a Preplanned out-of-TMA updates to TMA studies that don't meet evidentiary requirements for claims in advertising:

Efficacy and safety claims in HCP advertising require strong evidentiary support (e.g., randomization, rigorous control, blinding for subjective endpoints, type 1 error mitigation where relevant, and so on). The TMA is also considered strong evidentiary support even when the underlying study does not meet the customary evidentiary requirements for claims in advertising. As such, in alignment with section 1a above, out-of-TMA updates to TMA studies may support claims in advertising provided all of the following criteria are met:

- the evidentiary limitations in the update are the same as those in the original study approved by Health Canada
- the presentation is limited to the combination of endpoints and populations/subgroups featured in the TMA for the corresponding original study
- as in section 1.a above, they are pre-planned, published & peer-reviewed, and do not pertain to NOC/c products or class B opioid products

Note that for "special studies" and TMA studies that are not included among the pivotal trials, the study presentation in the APS must reflect the context, emphasis, and tone of TMA.

IMPORTANT: The fact that a study featuring one or more issues that potentially impair scientific validity or reliability was accepted into the TMA does not support promotion of other separate studies with similar issues/features.

2.b Loss of control arm

It is not unusual for studies to drop the control arm for the extension and follow-up periods. In this situation, the APS presentation of the extension/follow-up analysis must be:

- claim-neutral (i.e., informational)
- presented following the corresponding antecedent analysis (i.e., prior to loss of

the control arm)

External or historic controls must not be included in the APS presentation. See section 2.c for vaccine exceptions.

2.c Special consideration for vaccines: use of external control in long-term follow-up studies

Annex 1 has been added to clarify standards pertaining to the use of an external control in long-term follow-up studies for vaccine RCTs. Note that this Annex pertains only to vaccines.

3. The study duration must not increase the potential for harm relative to:

i. the information in the TMA

The Market Authorization Holder (MAH) is most aware of current and emerging safety data for its products. PAAB will require a signed letter from the medical department (or equivalent) attesting that the MAH is unaware of data, whether published or unpublished, suggesting that use of the product for the promoted study's duration might introduce new health risks or increase the frequency/severity of the health risks conveyed in the TMA.

ii. current medical practice:

All healthcare products have the potential to cause harm. This potential tends to increase with longer durations of exposure. Studies that are of longer duration than those of the studies in the TMA can only be used to inform HCPs about efficacy and safety when they are of **a duration of treatment that is already expected or typical for patients taking the product (or those from the same product class/category) for a given condition.**

The MAH's medical department (or equivalent) should provide an attestation that the typical or expected duration of treatment with a product or product class is not shorter than that of the out-of-label study and that they are unaware of factors that could impair applicability of this information to the promoted product.

Notwithstanding receipt of these attestations, the PAAB may consult with Health Canada on an as needed basis.

4. Existing directions for use in the TMA must enable the product to be safely and effectively used in the manner promoted in the APS

As an example, the PAAB may not accept clinical trials as evidentiary support for representations in advertising if their duration exceeds the time frame for which monitoring instructions are presented in the TMA.

Fictitious explanatory case for this requirement:

The longest study duration in Product XYZ's TMA is 6 months. A 2-year study evaluating efficacy in patients with the corresponding medical condition is submitted. The TMA contains a warning regarding red blood cell count and directs HCPs to measure the patient's red blood cell count according to one of the following schedules:

Scenario A *"At month 0, month 3, and month 6. Additional data is required to determine optimal testing frequency after 6 months of use".*		(The TMA must be updated prior to inclusion of data based on study duration that is beyond BOTH the longest pivotal trial for the corresponding use and 6 months).
Scenario B *"At month 0, month 3, and month 6".*		(The study may be considered. Additional considerations will be whether the MAH can provide evidence that monitoring is intended to end at 6 months. PAAB may need to consult with Health Canada)
Scenario C *"At baseline and every 3 months thereafter".*		(The study can be considered assuming all other requirements are met)
Scenario D *"Prior to treatment; further monitoring should be based on signs and symptoms"*		(The study can be considered assuming all other requirements are met)

5. The APS must include appropriate disclosures

Any disclosures necessary to ensure that the presentation is both truthful AND non-misleading must be prominently included in the APS.

As an example, cautions or directions relating to extended use must be disclosed.

Example: A statement similar to "The duration of this study is longer than that of data in the TMA" must be included.

Example: If the TMA indicates that the risk of an adverse outcome or toxicity increases with treatment duration, this information must be included.

Annex 1. Long-term follow-up for vaccine RCTs

Long-term follow-up studies for vaccines are often cited in guidelines as they help clinicians make evidence-based recommendations regarding the need/timing for booster doses. However, once a vaccine's efficacy has been established in a particular study population, it may no longer be justifiable to withhold a disease-preventing vaccine from patients who had initially been randomized to the placebo group. Consequently, vaccine trials that began as placebo-controlled randomized trials may undergo a pre-planned transition to an external/historic control for the comparator arm for long-term follow-up.

While external/historic controls generally increase the potential for bias substantially and consequently reduce the trial's validity and reliability, bias introduced through their use in longer term follow-up periods of well-designed long-term vaccine studies that began as placebo-controlled trials can be minimal/mitigated in the following circumstances:

- the study initially established efficacy in the evaluated population in a concurrent control setting (i.e., vs placebo)
- the historic/external control is used solely for placebo (i.e., comparisons against active comparators must always be concurrent and head-to-head within the same trial)
- the protocol for the external/historic control must have BOTH:
    - been pre-planned (or mandated e.g., by a government agency or ethics review board)
    - been documented in sufficient detail to demonstrate that appropriate steps were taken to mitigate the bias risks associated with the external/historic control

When the above criteria are met, the use of a historic/external control in a later stage of an RCT (i.e., in place of continuation of a concurrent placebo arm) will not, in and of itself, disqualify marketing claims of benefit from being considered. However, all other applicable requirements from the attached guidance document apply. The presentation must prominently convey the nature of the control arm (e.g., table column label, line plot legend, bar plot label, text bullet claims, and so on must all identify "historic placebo control" or equivalent).

The APS presentation must include the antecedent analysis (i.e., prior to loss of the concurrent control arm) prior to the findings of the extension/follow-up assessment.