

> SUBGROUP PRESENTATIONS... ON OR OFF THE TABLE?



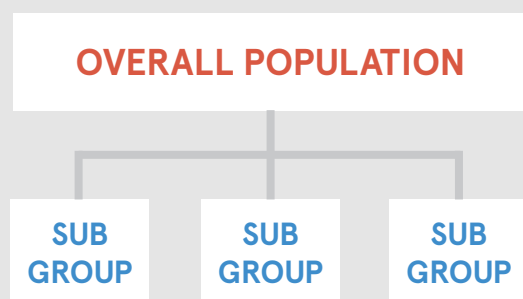
Corasón is a fictitious prescription drug for the treatment of heart failure.

Its **Terms of Market Authorization (TMA)** is a **product monograph (PM)**. The Clinical Trials section of the product monograph includes data from an **active comparison study** which can be described as follows...

- ▶ Evaluated population is within the boundaries of the Corasón indication
- ▶ Head-to-head versus the active comparator
- ▶ Robustly controlled to ensure the only difference between the treatment arms is the drug treatment
- ▶ Randomized with concealed allocation
- ▶ Double blinded
- ▶ Intention to treat analysis of all a priori defined endpoints



The PM includes the **overall population** data from this study in addition to data for **three subgroups** within the study.



There were a **dozen subgroups analyses** done in the study but only three appear in the PM.


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The efficacy of the sponsor's drug was **numerically higher** than the active comparator in two of the three PM sub-populations.


SUB GROUP


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> CASE 1

SEEKING A PAAB OPINION

The client submitted an opinion to the PAAB to learn whether the subgroups presented in the monograph can appear in an upcoming **APS submission** even though the study **had not yet been published**.



YES...IF:



The content from the product monograph appears in the APS in a manner which reflects the PM's **context** and **emphasis**.



The **PM is the only acceptable source** of content relating to this study (as it has not been published & peer reviewed per PAAB s3.1.1). Only the PM can be cited in reference to this study data.

> CASE 2

PAAB SUBMISSION PRIOR TO PUBLICATION OF STUDY

Encouraged by the above PAAB response, the client submitted an APS **referencing only the PM**.



The subgroup of patients **above the age of 60** only appears **once** in the PM. It appears in a **table** showing the observed efficacy for Corasón and that of the comparator in **three subgroups**.



Although no statistical analysis is presented, the **efficacy is numerically higher** for Corasón than the active comparator in patients above the age of 60. There is **no other mention** of this subgroup anywhere in the PM.



> CASE 2 CONTINUED

In order to reflect the low level of emphasis in the PM, the client included only a **single non-emphasized claim** stating that Corasón had demonstrated more efficacy on the studied endpoint than the active comparator along with a thorough presentation of the overall study sample results. **Is this acceptable?**



NO



The PM **does not support an inference of statistically higher efficacy** (neither through the inclusion of inferential statistics nor through inclusion of a statement inferring that the efficacy for Corasón is higher in this subgroup).



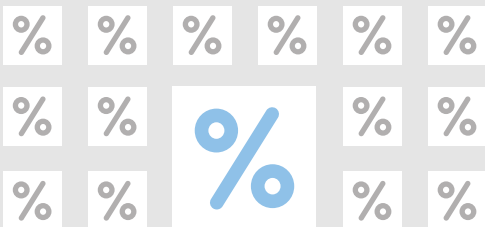
The PAAB therefore questioned the claim.



It's important to keep in mind that a **numerical difference is not necessarily a statistically significant one**. PAAB s5.9.



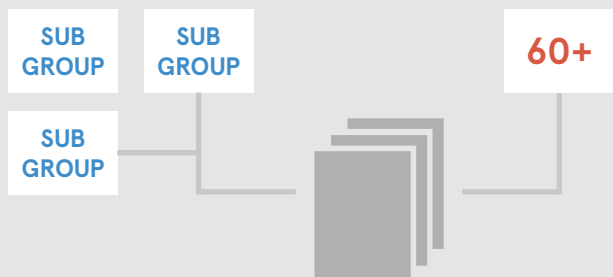
The **client's written response** clarified that the submission to Health Canada included statistical analysis. The client response included the corresponding data on file with the **statistically significant p-value highlighted** in order to direct the reviewer's eyes. **Does this alter the PAAB's position?**



NO



There is **no proof of approval** of the inferential statistics by Health Canada. The PAAB requested that the **presentation be revised** to include the subgroup of patients above the age of 60 along with the other subgroups from the PM table (i.e. rather than selectively singling out the data pertaining to this sub-population).



Additionally, the PAAB asked that the presentation be made **claim-neutral**. PAAB s3.1.



> CASE 3

PAAB SUBMISSION AFTER PUBLICATION OF STUDY

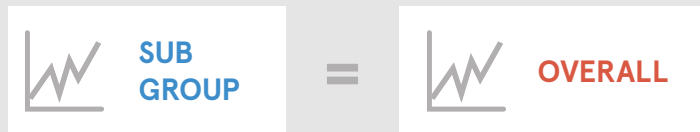
A few months later, the study is **published** in a highly regarded peer-reviewed journal.



Now that this additional reference can be considered as a **basis for claims**, the client submits a new piece including a **non-emphasized claim** relating to the subpopulation with concomitant diabetes. Data for this endpoint (which was defined a priori) is in the published trial but not in the PM.



The results in this **subpopulation** are **directionally aligned** with those in the overall study population. **Sounds like a slam dunk right?**



NO



Subgroup analyses are particularly vulnerable to **random error**.



For example, the need to perform **multiple inferential tests** (i.e. for each subgroup) contributes to their higher risk of **Type I errors**.



Two separate studies meeting all standards in the PAAB Code and guidances are generally required to **support claims** relating to subgroups that are within the limitations of the product's approved indication while not being explicitly discussed in the PM.



The claim was therefore questioned during the PAAB review. PAAB s3.1.9

The [guidance document](#) on the PAAB website outlines the provisions relating to subgroup analysis.

> CASE 3 CONTINUED

The **client's response** explained that, although there is no second study evaluating the sponsor's product in this subgroup, the results observed in this subgroup are **consistent with a biologic rationale** which appears in Canadian consensus guidelines.



Additionally, the client calls the reviewer's attention to a section of the published study in which **Bonferroni adjustments** were made (as planned a priori) on the p-value to address the increased risk of Type I error.
Might this change anything?



YES

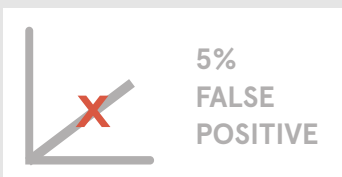


Let's provide some background information before explaining why.

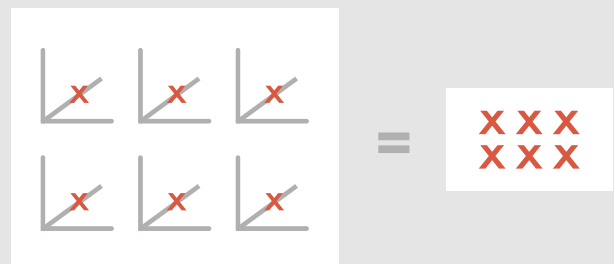
We'll risk over simplifying a bit for the sake of clarity...



Essentially, every time an **inferential test** is performed with a threshold for statistical significance of $p > 0.05$, there is a **5%** risk that a statistical significant finding will be observed for that particular test by **chance alone** (i.e. a "false positive" or "Type I error").



Therefore, the **larger** the set of performed inferential tests, the **higher the risk** that at least one of those observations of statistical significance from the set has occurred by chance alone.



This inflation in the risk of false positives can result in **unsubstantiated claims for the drug.**

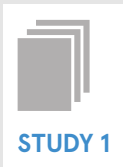


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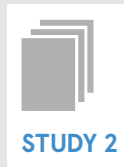


> CASE 3 CONTINUED

Replicating the study finding in a separate & independent trial is a **robust** way to demonstrate that a finding was unlikely to be due to chance alone. However, there are alternative manners of doing so.



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For example, case 3 involved the a priori selection of a **multiplicity adjustment strategy** (in this case the Bonferroni adjustment). The Bonferroni adjustment increases the **threshold for statistical significance** by a degree commensurate to the number of inferential tests performed on the data. The non-emphasized claim was ultimately accepted because the **p-value remained statistically significant** despite the robust multiplicity adjustment used to limit the risk of Type I errors.



The PAAB did require some adjustments to the claim to accurately convey the results and render the claim suitable. See the document "[Guidance on Subgroup Analysis](#)", available on the resources tab on the PAAB website for a more comprehensive look at subgroup specific claim requirements. PAAB s5.12 & 3.1.9.

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