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How to Best Define Target Populations of Medicines in View of Their Coverage by the National Health Insurance Scheme?

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Abstract – The target population of a medicine may include different populations that may partially overlap including the population that has been evaluated in the clinical trials, the population for which the medicine provides an actual benefit (SMR), that for which the drug provides an improvement of the actual benefit (ASMR), etc. The definition of the target population in both qualitative and quantitative terms has key public health and economic implications. Recommendations are made to shed light on the definitions, to clarify the requests of the public decision makers and to improve the methods and the sources allowing the quantification of target populations.

1. Introduction

Round Table n°5 was devoted to the definition of target populations for medicines with a view to their coverage by the national french health insurance scheme. The qualitative and quantitative definition of target populations is associated with major public health and economic stakes for the different parties involved – the pharmaceutical industry, payers, decision makers, evaluation agencies, and patients. Several of the parties involved have expressed their dissatisfaction regarding both the quality of the target population estimations or the data allowing their estimation, and the lack of transparency about the manner in which this information is being used at the different levels of the reimbursement decision process.

2. Definitions

A major part of the debates involved the definition of the term "target population" itself. This term is widely used in marketing and refers to a section of the population for which a product or service is intended. In the evaluation of a medicine, in particular with reference to its reimbursement, this term encompass different populations that partially overlap and that are defined and used for different ends by the different players [pharmaceutical industry, Ministry of Health, Economic Committee for Health Products (CEP), Transparency Committee, European Medicine Agency (EMA)] at different moments of the process, from the development of a medicine to its market launch and its coverage.

At the time of the introduction on the market, the target population is defined based on the results of clinical trials of the therapy administered for a given therapeutic objective. Although the population of these trials is supposed to represent the target population of the treating physician, it is only a sub-group of it (figure 1). One can never be entirely sure that the administration of the same therapy, under the same conditions, but to other individuals, would give the same results, precisely because those individuals are different (in particular, the patients included in trials are often at a lower risk). However, everyday medical practice is based on the

⋆ For the list of participants, see the end of the article.

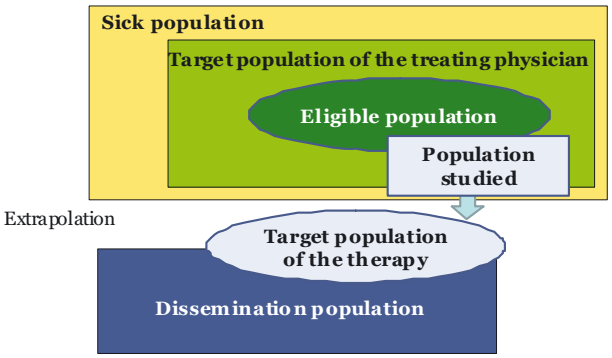

Fig. 1. Populations of interest. After Collet *et al.*[3]

inference of the efficacy of treatments on people who are different from those on whom they were tested.[1]

With regard to coverage status, Article R 163-18 of the French Social Security Code defines the target population as follows: "The estimation of the number of patients falling within the therapeutic indication(s) for which the TC deems the inclusion in the coverage list justified, according to the epidemiological data available. If necessary, the evaluation will mention the impossibility of carrying out precise estimations."

The standard coverage application documentation[2] identifies the populations to be described in the following manner:

"Define all patients falling within the therapeutic indication(s) and likely to derive a benefit from the treatment, excluding specifically:

- *The patients for whom a benefit has not been demonstrated.*
- *The patients presenting with a contraindication.*

Then describe the sub-groups of patients deriving a particular benefit from the proprietary medicine, for example those for whom an ASMR (improvement in actual benefit) is requested, if this is not the case for the entire target population.

Estimation of the target population falling within the indication(s).

Estimation of a sub-population able to benefit more particularly from the treatment".

It has also been emphasised that the target population of a product is not defined once and for all but that it may evolve over time according to various factors including changes in diagnostic techniques, screening strategies, available treatment strategies and treatment recommendations.

3. Current situation

3.1. Process for producing target populations

The opinions (evaluation reports) of the TC are prepared at the outset by the project manager of the given dossiers at the French National Authority for Health (HAS) in the form of a preparatory document supported by the opinions of two or three clinical experts, which is then discussed, approved and finalised by the TC (figure 2).

Table I. Examples of target populations estimates extracted from the Transparency Committee opinions published on the website of the HAS in the period January to July 2009.

Medicine	Target population
N...	14 000 to 18 000
E...	180 000 to 580 000
E...	56 000 to 500 000
R...	Maximum 15 000
T...	900
L...	796 000 (758 000 to 910 000)

3.2. Revues of estimated target populations

A systematic review of the paragraph entitled "target population" of all the opinions of the TC published on the HAS website from January to July 2009 has been performed.

Of the 130 opinions containing a "target population" paragraph, the target population could not be estimated at all in 15 (12%) and could only be estimated partly in nine (7%). In one third of the cases (n=42), the Transparency Committee opinion explicitly relied on expert opinion to estimate either the size of the target population as such or one of the key parameters used for this estimation (see examples below).

- Example 1. "The sub-population of resistant patients who may benefit from a treatment with [...] could, according to the experts, reach a maximum of 3000 patients in France".
- Example 2. "The percentage of patients presenting a contraindication to metformine accounts for about 10% of the population (expert opinion)".

It is noted that in 30% of the cases, the target population was estimated to be less than 10 000 people. The way target populations estimates are formulated and their levels of precision are highly variable, which reflects, at least partly, the quality of available data (table I).

Also, at the time of listing for coverage, in over 85% of cases, the population defined by the medicinal product's marketing authorisation (MA) corresponds to the population for which the TC had considered the actual medical benefit (SMR) of the drug as sufficient to justify its coverage, and also corresponds to the population for which the TC has established the level of improvement in medical benefit (ASMR). In some cases, the reimbursement population (SMR) is more restricted than that of the MA (figure 3). In such cases, the estimation of this population is of particular importance.

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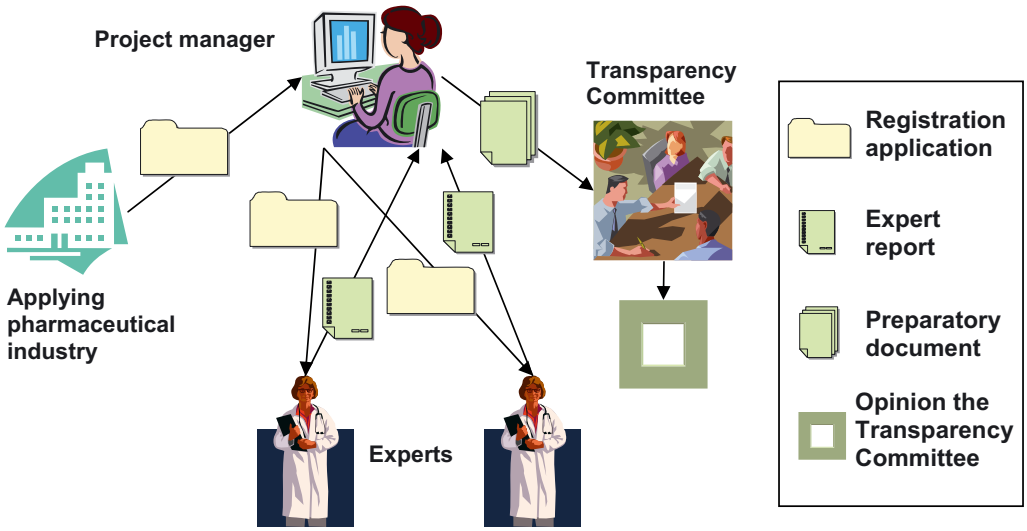

Fig. 2. Flow of production of the opinions of the Transparency Committee, Haute Autorité de Santé.

MA population	SMR population
"H is indicated for the treatment of moderate to severe psoriasis, in adult patients who do not respond to other systemic treatments such as ciclosporin, methotrexate or PUVA therapy, or patients in whom these treatments are contraindicated or poorly tolerated."	"The TC considers that the actual medical benefit provided by H is significant in patients with serious chronic psoriasis in whom at least 2 systemic treatments including phototherapy, methotrexate and ciclosporin have failed (non-responders, with a contraindication or who are intolerant). For other patients not responding to these criteria for treatment, the actual medical benefit provided is insufficient."

Fig. 3. Example of difference between the population of the market authorisation (MA) and the covered population (SMR population) for medicine H. **MA**: market authorisation; **SMR**: "service medical rendu" (actual benefit); **TC**: Transparency Committee.

It has also been found that in the great majority of cases, the "target population" of medicines was not re-evaluated by the TC when evaluating the reimbursement registration update application. Of the 83 opinions examined, 72 did not contain a "Target population" paragraph. However, a majority (66%) of the opinions had examined prescription data. These prescription data correspond to volumes (*e.g.* number of boxes) and in the majority of cases they were derived from the EPPM observatory (on-going survey on medical prescriptions) maintained by IMS Health. Of the 11 opinions with a "Target population" paragraph, the estimations have been revised on the basis of new data submitted. Where relevant, the results of the post-MA studies intended to better characterise the treated population are described in the CT opinions.

3.3. Use of target populations abroad

In order to explore the use of target population estimations and their effects on the price of medicines abroad, a questionnaire was sent by one of the Round Table participants, working for the pharmaceutical industry to their counterparts in other countries. The following six countries participated in the survey: Germany, Australia, Belgium, Spain, Italy and the Netherlands. The questions asked and the replies obtained are presented below:

- *Question 1. Are estimates of target populations required for reimbursement and/or pricing of drugs in your country?*
  An estimation is required in all of the countries except Germany.
- *Question 2. Do these estimates have a direct influence on reimbursement or pricing?*
  In the countries where the applicant has to provide an estimation of the target population, the expected budgetary impact has a direct effect on the prices of medicines. Insofar as it is one of the parameters that determines the budgetary impact, the population also has an effect, but in a more indirect manner, on the price of medicines (table II).
- *Question 3. What items should the estimations of target populations include?*
  It was found that in the five responding countries, the market shares need to be systematically provided. However, an estimation of the size of the sub-groups with expected supplementary benefits (*i.e.* ASMR) is only required in two countries out of five (table III).
- *Question 4. What types of information/data are used to produce and/or to support the estimations?*

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Table II. Influence of target populations estimates on reimbursement or pricing of medicines.

Country	Do estimates of target populations have a direct influence on reimbursement or pricing?
Australia	A company has to provide estimates of the financial impact on the Pharmaceutical Benefits Schedule (PBS - the national drugs list) per year for each of the 1st 4 years of usage (in situation that the drug is approved by the PBAC for PBS listing). A drug with large volume potentially has a big impact on the budget. This can lead to a pressure on the price requested, with PBPA often recommending a listing at a lower price (at which it would be even more cost effective).
Belgium	Volume (high incidence) has impact on the budget for the authorities. This can make pressure on the price.
Spain	Pricing and reimbursement negotiation requires a budget impact analysis so we need patient estimates. It is very important to give a good estimate as the Ministry in many occasions decides to review the figures provided by the companies and if the sales are significantly higher that the estimates, there is a risk of price decrease.
Italy	The highest the potential market the hardest is the negotiation process and challenges on price.
Netherlands	Estimates of target population are key input into a budget impact analysis that is required for reimbursement dossiers of products that are claimed to have therapeutic added-value, orphan drugs, or would be the only reimbursed drug for a specific indication. There are no formal criteria for how budget impact is assessed and how it will influence a reimbursement decision.

PBAC=Pharmaceutical Benefits Advisory Committee; **PBPA**=Pharmaceutical Benefits Pricing Authority.
Germany is not included in this table as the answer to the first question was no for this country.

Table III. Items that have to be provided in the estimation of target populations.

Country	Total population for the indication	Sub-groups by severity of the disease/medical condition	Sub-groups by type of therapeutic management	Sub-groups with expected supplementary benefits	Expected market shares
Australia	✓	✓	✓	✓	✓
Belgium	✓	✓			✓
Spain		✓	✓		✓
Italy	✓	✓	✓	✓	✓
Netherlands	✓		±		✓
Total	4	4	3–4	2	5

Germany is not included in this table as the answer to the first question was no for this country.

The type of information or data used to produce and support the estimations varies considerably from one country to another (table IV). The five responding countries often use national or local data and four countries out of six rely, to varying degrees of frequency, to the opinions of experts.

4. Conclusion

It was concluded that population estimations could be improved. Proposals have been made with a view to improving the qualitative and quantitative population estimations that have a significant impact on reimbursement discussions. These proposals are as follows:

- To clarify the debate, in particular, to no longer talk about a target population but to explicitly define the population of interest (*e.g.* MA population, population eligible for reimbursement, population receiving a particular benefit).
- To improve the dialogue between the parties involved in order to better share the objectives, the expectations and the items required for the decision; to determine what are the factors (*e.g.* volumes, price) that have the greatest impact on the level of discussion at the time of the product's inclusion in the list.
- To produce more epidemiological data useful for the estimation of the populations of interest and better share these data [*e.g.* support for measures of the strategic committee of health industries (Comité stratégique des industries de santé–CSIS), common portal for epidemiological resources, to encourage research in this area by research tax credit, to promote methodological research and the use of databases from the national health insurance scheme (*Caisse nationale de l'assurance maladie des travailleurs salariés - CnamTS*)].
- To improve estimation methods and, in particular, to formalise and to document the use of experts' opinion when need.
- To look ahead by focussing on situations requiring a particular action plan for the evaluation of the transparency dossier (*e.g.* medicines added on top of an existing therapeutic

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Table IV. Type of information and data used to produce and to support the target populations estimates.

Pays	Data source references	Ad-hoc data collection	Documented expert opinion	National/Local data	Justification/ explanation of hypothesis made
Australia	+++	+	++	+++	+
Belgium	+++	+++	++ (for sub-groups)	+++	+ (for market shares)
Spain	+			++	+
Italy	+++		+	++	
Netherlands	+++	+	+	++	

+++: very frequently; **++**: relatively frequently; **+**: rarely.
Germany is not included in this table as the answer to the first question was no for this country.

strategy, situations where data on disease frequency (incidence or prevalence) is missing, where the epidemiology is rapidly evolving or when the risk-benefit is not heterogeneous across the sub-populations for which the medicine is indicated.

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