From single-arm studies to externally controlled studies. Methodological considerations and guidelines

Michel Cucherat, Silvy Laporte, Olivier Delaitre, Jehan-Michel Behier, Anne d'Andon, Florence Binlich, Serge Bureau, Catherine Cornu, Cécile Fouret, Natalie Hoog Labouret, et al.

THERAPIES

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From single-arm studies to externally controlled studies. Methodological considerations and guidelines*

Single-arm studies

Michel Cucherat[a,*], Silvy Laporte[b], Olivier Delaitre[c], Jehan-Michel Behier[d], the participants of Giens XXXV Round Table « Clinical Research », Anne d'Andon[e], Florence Binlich[f], Serge Bureau[g], Catherine Cornu[h], Cécile Fouret[i], Natalie Hoog Labouret[j], Bruno Laviolle[k], Houda Miadi-Fargier[l], Xavier Paoletti[m], Matthieu Roustit[n], Tabassome Simon[o], Nathalie Varoqueaux[p], Eric Vicaut[q], Jérémie Westerloppe[r]

[a] *Service de pharmacotoxicologie, hospices civils de Lyon, 69003 Lyon, France ; Université Lyon 1, CNRS, UMR5558, laboratoire de biométrie et biologie évolutive, 69008 Lyon, France*

[b] *Unité de recherche clinique innovation pharmacologie, hopital Nord, batiment recherche, CHU Saint-Etienne ; UMR 1059 Sainbiose, Université Jean Monnet, 42022 Saint-Etienne, France*

[c] *Boehringer Ingelheim France, 75013 Paris, France*

[d] *Celgene, 92066 Paris La Défense cedex, France*

[e] *CEMKA, 92340 Bourg la Reine, France*

[f] *Servier, 92284 Suresnes, France*

[g] *AP-HP, 75010 Paris, France*

[h] *INSERM, CIC1407, hospices civils de Lyon, 69000, Lyon, France ; UMR 5558, université Claude Bernard Lyon 1, 69100 Lyon, France*

[i] *Medtronic France, 92100, Boulogne-Billancourt, France*

[j] *Institut national du cancer, 92513 Boulogne Billancourt, France*

[k] *Univ Rennes, CHU Rennes, service de Pharmacologie ; Inserm, CIC 1414, centre d'investigation clinique de Rennes, 35000 Rennes, France*

[l] *Bayer HealthCare, 59120 Loos, France*

[m] *Université de Versailles St-Quentin, INSERM U900, équipe de biostatistiques pour la médecine de précision et Institut Curie, 92210 Saint Cloud, France*

[n] *Univ Grenoble Alpes, HP2, Inserm, CHU Grenoble Alpes, 38000 Grenoble, France*

[o] *Service de pharmacologie clinique, plateforme de recherche clinique de l'Est parisien (URCEST-CRCEST-CRBHUEP-SU), Assistance Publique-Hôpitaux de Paris, hôpital Saint Antoine, Paris, France ; Sorbonne université, université Pierre et Marie Curie site St Antoine,*

75012 Paris, France ; FACT (French Alliance for CV Clinical Trials), réseau F-CRIN ; INSERM U1148, 75877 Paris, France

[p] *Astra Zeneca, 92400 Courbevoie, France*

[q] *Unité de recherche clinique, hôpital Fernand Widal, AP-HP, 75010 Paris, France*

[r] *Bristol-Myers Squibb, 92500 Rueil-Malmaison, France*

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*Corresponding author. Service de pharmacotoxicologie, hospices civils de Lyon, 162 avenue Lacassagne, 69003 Lyon, France.

E-mail adress: michel.cucherat@univ-lyon1.fr (M. Cucherat)

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Summary

Single-arm studies are sometimes used as pivotal studies but they have methodological limitations which prevent them from obtaining the high level of reliability as for a randomised controlled study which remains the gold standard in the evaluation of new treatments. The objective of this roundtable was to discuss the limitations of these single-arm studies, to analyse available and acceptable solutions in order to propose guidelines for their conduct and assessment. Single-arm studies themselves are intrinsically inappropriate for demonstrating the benefit of a new treatment because it is impossible to infer the benefit from a value obtained under treatment without knowing what it would have been in the absence of the new treatment. The implication is that comparison with other data is necessary. However this comparison has limitations due to 1) the *post hoc* choice of the reference used for comparison, 2) the confusion bias for which an adjustment approach is imperative and, 3) the other biases, measure and attrition among others. When these limitations are taken into account this should, first and foremost, lead to the conduct of externally controlled trials instead of single-arm trials as is proposed by the latest version of ICH E10. Moreover, the external control must be formalised in the study protocol with *a priori* selection of both the reference control and the formal method of comparison: test in relation to a standard, adjustment on individual data, a synthetic control group or matching-adjusted indirect comparisons (MAIC). Lastly, externally controlled studies must be restricted to situations where randomisation is infeasible. To be acceptable, these studies must be able to guarantee freedom from residual confusion bias, which is only truly acceptable if the observed effect is dramatic and the usual course of the disease is highly predicable.

Abbreviations

ICH International Council for Harmonisation fo Technical Rquirements for Pharmaceuticals for Human Use

Keywords: Single-arm study; Indirect comparison; Matching-adjusted indirect comparisons; Non-comparative; control group; External control studyMA marketing authorisation

MAIC matching-adjusted indirect comparisons

MD medical devices

NICE National Institute for Health and Care Excellence

TTP time-to-progression

TTP1 time-to-progression on standard treatment

TTP2 time-to-progression on targeted treatment

Introduction

The methodology of randomised controlled trials was designed to provide a reliable, bias-free assessment of the inherent efficacy and safety of treatments. There being no other methodology which can give the same level of guarantee, the randomised controlled trial remains the gold standard for the assessment of new treatments.

Single-arm studies involving therapeutic intervention consist of a prospective series of patients all receiving the test treatment. These studies provide an assessment of the value of the outcome criterion on-treatment only, "in absolute terms" (e.g. % deaths at 12 months). As there is no comparator treatment, the benefit of the new treatment in relation to that on placebo or a reference treatment is not documented. For this reason, single-arm studies do not directly provide evidence of the benefit of a new treatment. Nevertheless, increasing numbers of single-arm studies are proposed as "pivotal" studies to support marketing authorisation, reimbursement or practice changes, for both medicines and medical devices (MD) [see below].

The aim of this roundtable was to discuss the limitations of these studies, to analyse available and acceptable solutions in order to propose guidelines for their conduct and critical assessment.

Context and meta-epidemiology

Although no exhaustive meta-epidemiological review has been published, preliminary data show a large increase in the use of single-arm studies over the past few years. Among the assessments conducted by the National Institute for Health and Care Excellence (NICE) in the years 2000-2016, 22 out of 489 (4%) were based on a single-arm study, of which half were conducted in 2015-2016; 10/22 (45%) of these recommendations were positive [1].

In France, analysis of the transparency commission opinions between January 2017 and June 2019, revealed that, out of 75 opinions in oncology and haemato-oncology, 16 (21%) were based, among other things, on single-arm, non-comparative studies. In the case of rare diseases, the proportion was 22/67 (33%).

Single-arm studies as pivotal studies are currently used in a variety of contexts. In the case of medical devices (MD), single-arm studies provide a way of assessing changes made to a device the value of which has been initially demonstrated by a randomised clinical trial. Similarly, in the case of rare diseases, these studies are sometimes chosen as the only pivotal study due to the small number of patients available for conducting randomised clinical trials.

However single-arm studies can also be the basis for certain marketing authorisations (MA) although they were conducted in fields where it would have been possible to perform randomised controlled trials (or when these are on-going in the case of fast-track registrations). The problem is the question of "forcing the hand" to ensure they are taken into account to gain market access and for the development of clinical guidelines.

Externally controlled studies are used in the assessment of treatments for rare diseases, for which recruitment is difficult due to their heterogeneity and small patient populations. One example is four phase 2 studies which assessed the efficacy of imatinib in cutaneous fibrosis of patients with systemic scleroderma. Three of these studies were conducted on an open-label basis without control

group. The results showed a decrease in cutaneous fibrosis (evaluated by the Rodnan skin score) after 12 months of treatment with imatinib (NCT00613171) [2]. In contrast, the fourth phase 2 trial, which was randomised, controlled and double-blinded, failed to demonstrate superiority of imatinib over placebo in cutaneous fibrosis; whereas there were more adverse effects in the imatinib group [3]. In view of these results, imatinib did not proceed to phase 3 testing. More recently, tocilizumab was assessed in the same indication but the phase 2 trial was randomised and controlled [4].

It is however probable that increasing numbers of externally controlled studies will be used in rare diseases, similar to the numbers observed in oncology. Indeed, a recent document from the Food and Drug Administration (FDA) presents the specificities and offers guidance on externally controlled studies (which they call *Natural History Studies*) in the context of rare diseases [5].

The methodological limits of single-arm studies

When there is no comparison with a control group, it is impossible to know if the value of the outcome criterion observed on treatment is better than that which would have been observed without this treatment in the same study: same patients, same outcome criterion measurement, same follow-up, same treatment setting.

The only situation where it is reasonably possible to draw a conclusion with no comparator is the so-called "100%/0%", corresponding to situations where some favourable outcomes or even the complete suppression of negative outcomes are observed on treatment in a pathology where the outcome with the reference treatment would be negative in 100% of cases. This is also the American NCI recommendation for combination therapies [6]. Single-arm studies should therefore be restricted to cases where the activity of the reference treatment is minimal, and randomisation infeasible. This type of situation is exceptional: even, for example, in the case of Ebola virus infection, the prognosis, although very poor, is not sufficiently dark to correspond to the 0%/100% rule because there are certain cases of spontaneous survival. A randomised trial was therefore performed to assess the clinical efficacy of ZMapp in Ebola virus infection [7].

Therefore the use of single-arm studies to demonstrate the benefit of a new treatment necessarily implies comparison which must call upon an external reference comparator (e.g. a historical control). Several types of external controls can be envisaged (cf. Table 1), and also meta-analyses when several identical studies are available ([8] for an example of meta-analysis performed for this purpose).

From a methodological viewpoint, the use of an external control has several significant limitations.

1) The reference comparator is often chosen *post hoc*: for this reason, there is no guarantee that the comparator was not deliberately selected to prioritise the new treatment. These studies must no longer be designed as single-arm descriptive studies, but as true comparative studies with a predefined external control group: the specified objective being the demonstration of the clinical value of the new treatment and not the simple description of the outcome of patients on treatment. After an inventory of all existing cohorts, including a systematic literature review, the choice of reference comparator will be specified in the protocol design, in the same way as the analytical

method, thus preventing any *post hoc* choice. The selection of the comparator cohort(s) must be discussed. This approach is in fact endorsed in the new version of International Council for Harmonisation of Tehcnical Requirements for Pharmaceuticals for Human Use (ICH) E10 which proposes the term externally controlled trial [9]. Moreover, the selection of reference comparator *a priori* at the time of study protocol design also reduces bias by using, for example, the same outcome criterion and the same method of measurement (see below). Ideally, individual patient data should be available to provide better handling of confounding factors (Propensity scores, multivariate analyses, etc.) and this point must be taken into account in the choice of external controls.

2) The other major limitation to the use of external controls is confusion bias: there is nothing to guarantee that the compared groups or results are comparable in terms of patients. For this reason several methods of formalising external controls (also called indirect comparisons, unanchored indirect comparisons) have been proposed in an attempt to increase the reliability of the conclusions drawn from externally controlled studies [10-13]. The objective of all these approaches is to compensate for the absence of a control by a design in which confounding factors are taken into account in the analysis. **Theoretically**, the methods eliminate confusion bias on condition that absolutely **all** confounding factors can be taken into account (factors that affect the outcome criterion and the difference in distribution between the treated cohort and its control group, including effect-modifying variables [14]). For this, potential confounding factors of each outcome criterion must first be identified by a systematic review of the prognostic studies. The adjustment (irrespective of the method) must take all these factors into account and they must also be predefined in the protocol. In order to confirm that these adjustments have achieved the intended goal, the size of the residual confusion bias may be estimated by the use of negative controls such as falsification of variables and by bias analysis [15]. Given the difficulties encountered in providing these guarantees, the results will only be convincing in the case of very significant results, which cannot be solely explained by biases and residual confusion. The selection of the reference comparator *a priori* at the outset of protocol design will also contribute to minimise the confusion bias, by matching the eligibility criteria with those used for the construction of the external control (restriction approach). This limitation due to confusion bias means that from a regulatory view point, the ICH E10 guidelines envisage the use of externally controlled studies only in very specific situations: “use of the external control design is restricted to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable”[16].

Other limitations exist which are measurement, selection and attrition biases.

Table 2 summarises these limitations and possible solutions. These biases are inherent in the design and cannot be corrected by statistical analyses. Assessment of the risk of bias using the ROBINS-I tool should provide an assessment of the degree of confidence which may be had in the results.

In common with randomised controlled studies, an externally controlled study must also ensure the clinical relevance of the comparison: relevant primary outcome criteria, comparator faithfully representing the approved standard of care at the time the decision was taken, follow-up period, safety assessment. In other words, **the study must be comparable in all these points to those of a pivotal randomised trial**.

Methods of formalising external controls

Comparison with a standard

The simplest form of formalisation of the external control is the statistical comparison with a reference value, predefined in the protocol and theoretically representing the value expected without the new treatment. This approach is restricted by the impossibility to adjust the reference value in relation to the characteristics of the patients actually included and by the possibility that the value chosen underestimates the performance of the control treatment. The protocol must therefore give a solid justification for the choice of this value, in particular by a systematic literature review.

Adjustment with aggregate data or matching-adjusted indirect comparisons (MAIC)

In the method of matching-adjusted indirect comparisons (MAIC) [11,12,14] the external control may be, for example, the aggregate data from a publication (historical cohort, pivotal clinical trial of the reference treatment, etc.). It provides an adjustment by reweighting the single-arm study patients (for whom individual data are available) to make them comparable, on the basis of available variables, with the population of the publication. The adjusted result of the treated cohort thus becomes comparable, to a certain extent, with that reported in the reference publication and an estimate of the impact of the new treatment can be made.

Adjustment with individual data

When the individual data are available for the external control (cohorts, control groups of reference treatment trial(s), etc.), the comparison may use the same adjustment techniques as observational pharmaco-epidemiological studies for example. The adjustment may be done by matching, stratification, regression or reweighting using the potential confounding factors themselves or a propensity score as covariates. This approach is certainly the most likely to eliminate confusion bias if all confounding factors have been taken into account.

In this setting, the approach of synthetic control groups™[1] is widely employed. In a generic way, it consists of extracting from a reference cohort (e.g. medico-administrative databases, hospital data warehouses, etc) a sample of patients matched to the patients of the single-arm cohort treated with the new treatment.

However, the use of a pre-existing reference cohort followed up at the same time as the single-arm study, brings up the problem of the impossibility to randomise and makes an assessment based on a single-arm trial difficult to accept.

Other methods

Sometimes other approaches are used such as before/after comparisons or simulations of the missing control arm, called simulated treatment comparison [12].

Before/after comparisons can be particularly biased, notably by selection bias, because inclusion in the treated cohort is often conditioned by the previous outcome of the patient (e.g tolerance or failure to respond to previous treatment). In oncology for example, Von Hoff proposed to assess the impact of a new targeted treatment on the time-to-progression (TTP) in patients with resistant illness by using the patient as his own control [17]. These patients received the targeted treatment after disease progression is observed on standard treatment. The TTP on targeted treatment (TTP2) is compared with the TTP on standard treatment (TTP1). It is a sort of non-randomised cross-over plan of the sequence to control the time effect. Given the hypothesis that (i) the cancer is increasingly aggressive with time and (ii) that multiple resistances develop, it would be expected that TTP2<TTP1 (or the ratio TTP2 / TTP1<1). Von Hoff suggested that a ratio > 1.3 was an indicator of an individual patient benefit. However, these hypotheses of a natural history of disease acceleration for all patients are contradicted by recent studies [18,19]. TTP1 is poorly predictive of TTP2 and thus this ratio is not well correlated to overall survival.

The simulated treatment comparison approach uses modelling of the outcome criterion from data of the treated cohort, modelling the predictive performance of which is not itself verifiable.

[1] The term “synthetic control arm” is a registered trade mark of Medidata Solutions, Inc.

Recommendations

- The randomised controlled trial remains the reference method for the assessment of new treatments, formalised external controls do not provide the same guarantees of reliability of the results, nor do they give the same level of proof.
- The possible resort to the use of an externally controlled trial must be robustly justified by unquestionable arguments.

Two situations have been identified: the initiation of a new study and the *post-hoc* utilisation of a previously completed study; but a first recommendation is common to both these situations:

Guidelines for a new study design

- Design the study as an externally controlled study (and not as a descriptive single-arm study): the initial objective of the study will be to demonstrate the benefit of the new treatment in comparison with the external control.
- Guarantee the clinical relevance of the outcome criteria, comparator treatments, patients included as for a pivotal study used for marketing authorisation, reimbursement or practice changes.
- Determine and justify the choice of external control *a priori*, with a systematic literature review to find all published cohorts, and the inventory of existing cohorts.
- Prefer external controls on which adjusted analyses may be performed: i.e. those for which there is access to individual data, or published cohorts with the best documentation.
- Document potential confounding factors *a priori* by a systematic review.
- Define *a priori* the strategy to evaluate residual confusion bias.
- Specify *a priori* a control and discussion of the biases (measurement, selection, attrition).

- Define *a priori* the statistical plan for analysis (detailed description of the choice of method, sensitivity analyses).
- All these elements must be included in a protocol, which will be dated and registered in a database such as ClinicalTrials.gov.

Guidelines of the *post hoc* use of a previously completed study

This situation corresponds to a very degradated methodology and should be avoided. In many cases it will be impossible to raise the level of proof of the study, because by definition all comparators and methods, will have been defined *post hoc*, and it is impossible to provide guarantees which exclude choices influenced by the results. In an attempt to remove as far as possible the pitfalls intrinsic to *post hoc*, the roundtable recommends:

- To document all foreseeable controls for this study: systematic review of published aggregate data (patient cohorts, control-arms of studies, etc.) and to list all existing patient cohorts which could potentially be used as external controls.
- To test the robustness of the results by showing that the vibration of the results leads to the same decision, irrespective of the control used.

Conclusion

Single-arm studies are intrinsically unsuited to demonstrate the benefit of a new treatment, because it is impossible to infer this benefit from a value on-treatment without knowing what it would have been in the absence of the new treatment.

To fulfil this objective, it is essential to perform this comparison: if it is not planned to conduct a comparative study versus an internal control group, the only possible alternative is to perform this comparison using an external control. In this setting, studies must no longer be purely descriptive simple single-arm studies, but must be designed like true controlled studies, with an external control group. The design of these studies must avoid any *post hoc* comparison, which would strongly challenge the validity of the resulting conclusions. Even if this is done, the results obtained are strongly compromised by the presence of confusion bias related to the non-comparability between treated cohort patients and those of the external control. To be acceptable, these studies must guarantee the absence of residual confusion bias. It must also be possible to rule out the presence of

other biases (measurement, selection and attrition). Lastly, the effect must be significant enough to not be the sole consequence of residual confounding factors or biases.

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SL No conflict of interest

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AA No conflict of interest

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References

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1] Anderson M, Naci H, Morrison D, Osipenko L, Mossialos E. A review of NICE appraisals of pharmaceuticals 2000-2016 found variation in establishing comparative clinical effectiveness. J Clin Epidemiol 2019;105:50-9.

[2] Spiera RF, Gordon JK, Mersten JN, Magro CM, Mehta M, Wildman HF, et al. Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label clinical trial. Ann Rheum Dis 2011;70(6):1003-9.

[3] Prey S, Ezzedine K, Doussau A, Grandoulier AS, Barcat D, Chatelus E, et al. Imatinib mesylate in scleroderma-associated diffuse skin fibrosis: a phase II multicentre randomized double-blinded controlled trial. Br J Dermatol 2012;167(5):1138-44.

[4] Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387(10038):2630-40.

[5] Food and Drug Administration. Rare diseases: natural history studies for drug development. Guidance for industry. 2019. https://www.fda.gov/media/122425/download. [Accessed 22 november 2019 (22 pp.)].

[6] Foster JC, Freidlin B, Kunos CA, Korn EL. Single-arm phase ii trials of combination therapies: a review of the CTEP experience 2008-2017. J Natl Cancer Inst 2019 Sep 23 pii: djz193.

[7] Group PIW, Multi-National PIIST, Davey RT, Jr., Dodd L, Proschan MA, Neaton J, et al. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med 2016;375(15):1448-56.

[8] Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 2008;26(4):527-34.

[9] Choice of control group and related issues in clinical trials E10. ICH harmonised tripartite guideline: International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. 2000. https://www.ich.org/. [Accessed 22 november 2019].

[10] Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. Med Decis Making 2018 Feb;38(2):200-211.

[11] Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health 2012;15(6):940-7.

[12] Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010;28(10):935-45.

[13] Caro JJ, Ishak KJ. No head-to-head trial? simulate the missing arms. Pharmacoeconomics 2010;28(10):957-67.

[14] Phillippo DM, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. NICE DSU technical support document NICE. Decembre 2016. http://nicedsu.org.uk/wp-content/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf. [Accessed 22 november (81 pp.)].

[15] Geenland S, Lash T. Bais analysis. In: Rothman K, Greenland S, Lash T, (Eds.), Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams and Wilkins 2008:345-80.

[16] ICH. Choice of control group and related issues in clinical trials E10. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. 2019. https://www.ich.org/. [Accessed 22 november 2019].

[17] Von Hoff DD, Stephenson JJ, Jr., Rosen P, Loesch DM, Borad MJ, Anthony S, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. J Clin Oncol 2010;28(33):4877-83.

[18] Watson S, Menis J, Baldini C, Martin-Romano P, Michot JM, Hollebecque A, et al. Time to progression ratio in cancer patients enrolled in early phase clinical trials: time for new guidelines? Br J Cancer 2018;119(8):937-9.

[19] Buyse M, Quinaux E, Hendlisz A, Golfinopoulos V, Tournigand C, Mick R. Progression-free survival ratio as end point for phase II trials in advanced solid tumors. J Clin Oncol 2011;29(15):e451-2.

Table 1. Types of possible external controls.

• Standard, reference value which may be either fixed by a "regulatory requirement", or arising from the literature (e.g. a cohort study) or a consensus conference • A cohort available in the form of a publication (individual data inaccessible) or a publication of a randomised trial one of the groups of which can be used as external control which could be the basis of a MAIC • A cohort with access to individual data which could be used for an observational type study approach • Randomised trial with access to individual data which could be used for an observational type study approach

MAIC matching-adjusted indirect comparisons

Table 2. Methodological limitations to external controls and possible solutions

Methodological limitations	**Possible solutions**
No control group, impossibility to determine the efficacy of the test treatment	Perform externally controlled trials instead
Post hoc selection of the reference control	Include the choice of reference control *a priori* in a protocol design at study outset
Confusion bias of the external controls	An adjustment method to be defined *a priori*, during study design, ensuring that all potential confounding factors, identified from a systematic review of all prognostic studies, are taken into account. The other variables which affect patient outcomes (setting, socioeconomic variables, treatment practices) must also be considered as potential confounding factors
Measurement bias	Align the externally controlled study protocol with that of the study used as comparator (same definition of criterion, same measurement method, etc.)
Selection bias	Avoid before/after comparisons
Attrition bias	Use a good quality external control which conducted a thorough follow-up of patients (low attrition rate)
Residual confusion bias	Specify negative controls as falsification of variables and an evaluation of the robustness of the result in relation to confounding factors not taken into account and other biases (bias analysis)