ASCERTAIN

UNCERTAIN DATA IN REGULATORY APPROVALS FOR MARKET AUTHORIZATION

WHAT IS THE BEST EVIDENCE TO HAVE FOR APPROVING A NEW MEDICINE FOR MARKET AUTHORISATION?

The evidence required (by the European Medicines Agency-EMA) for recommending a new medicine for market authorisation (a medicine can be sold on the European Union market) is obtained from **clinical trials**. These are research studies which test whether new medicines work and are safe. They are tested on volunteers, either patients or healthy persons. Usually, the new medicine will be tested against a control, which can be another medicine already in use or an inactive substance (placebo).

It should be noted here that **EMA does not authorise new medicines** but only assess the evidence and **make recommendations for authorisation**. The **final decision** on whether or not to grant a new medicine market authorisation belongs to the **European Commission**.

There are many types of clinical trials. The ones that are called **randomised controlled trials (RCTs)** are considered "gold standard" because they offer the evidence with the highest quality. They are called "randomised" because people involved in the study will be randomly assigned to either the treatment group or the control group. Randomisation and larger number of patients, as well as other measures, are taken to ensure that the **differences observed in clinical outcomes** between the two groups can **only be due to the differences in treatment received**.

RCTs are often conducted later in the development of a new medicine (usually in phase III clinical trials) and they include a larger number of patients than other trials in earlier phases.

Testing cancer medicines has a few particularities. For ethical reasons, it is **very rare that a placebo can be used**. Usually, the new medicine is tested against the existing **standard of care** (the usual/best available treatment doctors currently use), which can be different in different countries. No healthy persons are involved either, the **trials include only patients**. For rare cancers the number of patients involved in clinical trials can be small as the **patient population itself is small**. Together, these factors can make the results from cancer clinical trials less clear, so there is **more uncertainty** in the information available.

WHAT IS UNCERTAINTY IN CLINICAL DATA?

It is when the quality of the data **does not allow drawing conclusions** on the relationship between use of the new medicine and effect with a high degree of certainty. The uncertainty in the clinical evidence means that the **real-world benefit** of the new treatment might be **smaller or larger** than the evidence indicates, or **side effects** might be **more or less common** than we currently know. Aside from the use of different comparators or a smaller number of patients, mentioned above, uncertainty can come from **reliance on intermediate or surrogate endpoints**. Surrogate endpoints are clinical measures used in clinical trials to predict final outcomes, like survival. Although final outcomes give data more certainty, it might not be ethical to wait for a long-term clinical endpoint like death to be reached before determining if a treatment is working.

Regulators sometimes approve medicines with remaining uncertainty but **require more data after approval** (e.g. conditional approvals, post-marketing studies). Sometimes regulators accept more uncertainty to allow **earlier access to promising treatments**, particularly for serious or rare conditions. There needs to be a balance between getting access quickly and having very solid long-term evidence.

WHEN IS NON-RANDOMISED DATA USED IN REGULATORY APPROVALS?

Sometimes, conducting RCTs is **not feasible or even ethical**. They require a lot of time, energy and money, as well as a large group of patients to enrol. These conditions might not be possible nor ethical, for example, for **rare diseases** or diseases linked to a **short life span**. In cases when RCTs are not possible, other type of non-randomised methodologies are accepted instead in approving new medicines. They can include **Single Arm Trials** (SATs), (called single-arm trials because they have no control group) and **observational studies** with Real World Data (RWD) (such as electronic health records or population-based surveys used as an "external" control group for SATs). Non-RCTs and RWD can increase level of uncertainty associated with the effect of the new medicine compared with the standard of care.

HOW TRUSTWORTHY IS NON-RANDOMISED DATA?

Non-randomised data can be untrustworthy because of concerns for **bias**. Bias means that the **effects observed** in the data are **not caused by the treatment itself**, but other reasons such as patient characteristics (e.g., people who receive the new drug might be younger or fitter, so they would do better anyway).

With data from a RCT, the bias (factors that can distort the effect of a new medicine) is reduced to a minimum (not completely eliminated). Thus, RCTs can provide the **true effect of a drug**, albeit under ideal conditions. While non-randomised data has more bias, they can provide some **useful information about the effects** of the new medicine **under real-world conditions**. Such biases can be addressed by the use of advanced analytical methods. The trustworthiness of non-randomized data ultimately **depends on how well these biases are understood and addressed**, to increase the confidence in the new treatment's benefits.

SINGLE ARM STUDIES: WHAT ARE THEY AND WHEN ARE THEY USED?

Single arm studies include only one treatment group (or arm) that receive the medicine to be assessed and they **do not include a control group** (there is no direct comparison). Single arm studies can be either **interventional** (a therapy is being actively administered to a group to assess its clinical effect) or **observational** (researchers observe participants receiving the treatment in their own settings without influencing the treatment or conditions participants experience). Thus, single arm studies are **non-randomised**. They are used in certain cases in the regulation of new medicines. In the majority of cases, single arm studies are used in the **conditional marketing authorizations** of certain medicines to address an unmet medical need (like medicines for rare diseases). However, single-arm studies **must still show clear clinical benefit**. Their results are usually interpreted together with other information, for example data from similar patients who received standard care, to better understand how meaningful the benefits are.

WHAT ARE INDIRECT COMPARISONS AND HOW ARE THEY USED IN DECISION-MAKING?

Indirect comparisons are in many cases **accompanying the use of single arm studies** in regulatory approvals. They are called 'indirect' because the treatments have not been tested against each other in the same clinical trial. Instead, **results from different studies** are used. For example, if treatment A was tested against a standard treatment C in one study, and treatment B was tested against the same standard treatment C in another study, we can indirectly compare A and B through their separate results versus C.

To do this comparison, researchers may use **real-world data** (such as information from patient registries or hospital records) and **advanced statistical methods** to adjust for differences between the studies and make the comparisons more reliable (to reduce potential bias).

HOW ARE NON-RANDOMISED METHODOLOGIES USED IN THE MARKET AUTHORIZATION OF NEW MEDICINES?

It is important to remember that RCTs, especially those that measure how long patients live (**overall survival**), are still **the preferred type of evidence** for approving new medicines.

Non-randomised data are usually used as **supporting evidence**. In some situations, such as **accelerated or conditional approvals**, they can be used as the main evidence, but then more data from RCTs or other studies is usually required later. When regulators rely on non-randomised data, they expect to see a **large and clear benefit of the new treatment** compared with existing options, and they check that researchers have taken steps to reduce bias and errors. They also consider other aspects, such as **how serious the condition** is and **how big the unmet medical need is**, when making their final decision.

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