# Conducting Clinical Trials in Austria

## Offers a Fully Incorporated GCP Environment

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**When Austria updated national legislation and assumed EU member state status, it opened up new opportunities for sponsors and CROs. This ethics committee chair analyzes the country's revamped research landscape and offers guidelines for initiating studies.**

Clinical trials in Austria have had an inconstant history. Until the early 1980s, pertinent legislation was essentially nonexistent. That situation attracted a substantial volume of clinical research to Austria because other countries had begun to heavily regulate such activities.

Austria's Ministry of Health (MOH) soon reacted to what it perceived as its overly liberal climate, passing the Austrian Medicines Act of 1984. The law required that a sponsor must obtain a positive opinion from a government advisory body (the cumbersome Drug Advisory Board, or "Arzneimittelbeirat") before initiating most clinical trials.

Though well intended, that regulatory process proved exceedingly inefficient and unpredictable, stifling both industry-sponsored and investigator-initiated clinical research. Very quickly, the international clinical trials community shunned Austrian research centers, which resulted in the loss of many industry-related jobs.

Yet in many ways, 1994 was a significant turning point for clinical trials in Austria. Realizing that the pendulum had swung too far—and because Austria had become a full member of the European Union (EU) in 1996—the government seized upon the opportunity to shape a new medicines act that would integrate many of the factors included in the EU's good clinical practice (GCP) guideline of 1990. [1] Thus, Austria became one of the first EU member states to fully incorporate GCP guidelines into national law.

Though bad memories of the old "Arzneimittelbeirat"-days may linger in some minds, the current legal and administrative framework basically supports an efficient environment for conducting clinical trials in Austria. For now, the pendulum sits about in the middle.

Legal requirements for conducting clinical trials are laid down in Austrian federal laws. Those regulations include the Medicines Act of 1994, the Medical Device Act of 1996, the Hospital Act of 1993, and, to a lesser extent, other state legislation. Although the European Commission's new directive on clinical trials (which is currently in the making) will likely necessitate some minor amendments to Austrian legislation, no major reshuffling of the legal framework is anticipated. Hence, conditions for clinical trials appear predictable for the near future and reasonably beyond.

### Initiating a clinical trial

Documentation that Austria usually requires for launching a clinical trial appears in the table. The initial question a prospective sponsor of a drug study must answer is whether "relevant clinical information" is available for the drug slated to undergo research.

An MOH directive constitutes how relevant information is defined. Essentially, any previous clinical trial that has been conducted and reported under GCP criteria will qualify provided that drug dosage, duration of treatment, and other factors bear any kind of scientifically meaningful relationship to the treatment schedule for the planned trial. If such previous experience is available and properly summarized in a study report there is no reason for the Drug Advisory Board to become involved. Therefore, besides obtaining ethics committee approval, the only official requirement for those trials is to notify the MOH.

That notification takes place by mailing a standard form along with the latest version of the trial protocol and informed consent sheet. After the mailing date, a 28-day waiting period is "strongly recommended," states an MOH directive. During that time, the MOH may raise objections to the trial although experience shows that to be a rare event. Because notification may be carried out simultaneously with ethics committee submission, the waiting period thus poses no inevitable obstacle to trial progression.

After a sponsor obtains ethics committee approval, the final administrative procedure that may be required before starting the trial is to request an import license for trial medication. That requirement may be waived, however, if the drug to undergo study is already licensed in Aus-

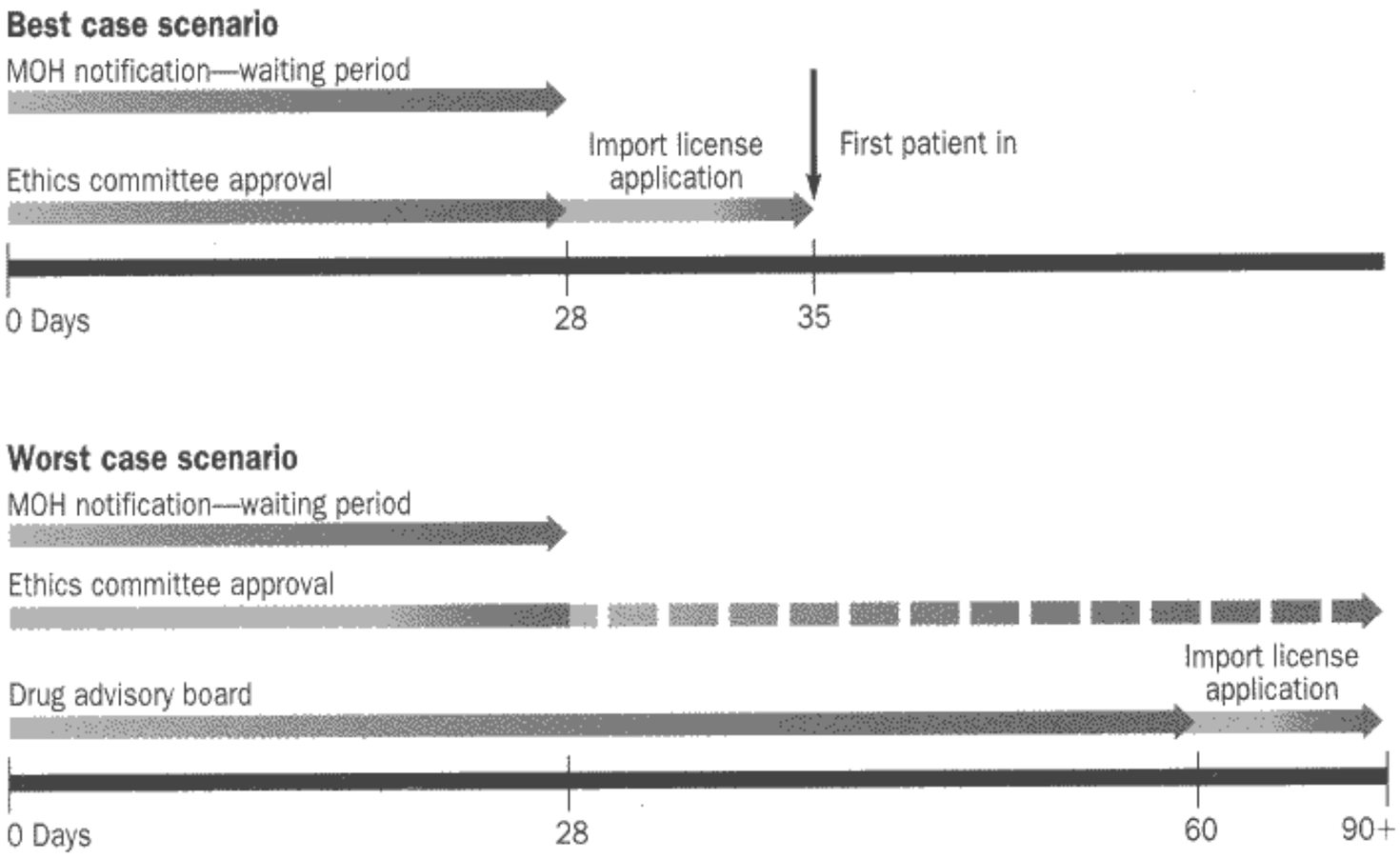


**Figure 1.** After obtaining ethics committee approval, the final administrative procedure that may be required before starting a trial in Austria is acquiring an import license for trial medication. This approach applies to almost all trials initiated in the country.

tria, such as often occurs with Phase 4 studies.

In practice, this simplified regulatory approach probably applies to more than 95% of all trials initiated in Austria. That capability enables the potential best-case scenario that appears in Figure 1.

### Time lines to trials approval

In the absence of relevant clinical information on the study drug (a situation that usually means the product is entering Phase 1 trials) a sponsor must seek a positive opinion in writing from the Drug Advisory Board. Although that process is more time-consuming than the process for a product with trial data already on record, it holds no comparison with the old Arzneimittelbeirat: Today's law now limits the response time of the board to two months, whereas the previous time line of the old Arzneimittelbeirat extended up to six months. In addition, ethics committee submission may be done simultaneously. Nevertheless, pretrial administration in these cases may take up to three months, as the worst-case scenario illustrates in Figure 1.

That longer procedure does not necessarily apply to all Phase 1 studies, however. The law makes no distinction between trials in various phases of development or those involving healthy volunteers versus patients. Thus, in the hands of an experienced trial administrator, the lag-time between compiling a complete trial dossier and "first-patient-in" may be as little as 35 days, provided there are no controversial scientific or ethical issues (Figure 1).

Rules for device trials, based on the EU directive 93/42/EEC, are slightly different from those for drug product trials. For device trials, the waiting period is 60 days after MOH notification and no equivalent process exists that parallels the Drug Advisory Board rule that applies to drug trials.[2]

### Ethics committees

Independent ethics committees are firmly established in Austria.[3] National legislation concerning their constitution, statutes, maximum response time (two months for drug studies and three months for device studies), and other parameters were modeled on the original EU GCP guideline. In fact, the regulations closely follow the current, proposed EU directive on clinical trials.

Today there are regional committees in most of the states that make up Austria's federal republic, but the notable exception is Vienna. As the nation's capital and biggest city, Vienna is also home to most of the hospitals that are active in clinical research. More than 15 committees currently operate there, and that kind of coexistence of several ethics committees—though similar to that of other EU member states—can be annoying to those who conduct multicenter trials. But at least these university-based committees have mutual recognition agreements in place.

Though most of the existing ethics committees throughout Austria have adequate experience in handling monocenter and multicenter clinical trials, there may be substantial differences in their various response times. More importantly, they may offer contradictory votes on the same multicenter trial protocols.[4] Efforts are under way to remedy that deficiency through widespread adoption of existing mutual recognition agreements and perhaps by instituting a national ethics committee.

Nevertheless, the binding requirement by the draft directive that requires each EU member state to furnish a single ethics committee opinion for a particular trial will greatly help this process.[5]

The MOH initiated inspections of drug trials in 1995, and, so far, trials are selected for inspections through a randomization procedure. Once a trial has been selected for inspection, an experienced trial auditor/inspector visits both the sponsor and the investigator site. Experience shows that inspections are comparable in scope to sponsor-initiated audits.

### Building an investigator base

There are no legal limitations on where clinical drug trials may be conducted in Austria. The law merely stipulates that investigators must be fully trained in their respective fields of medicine (or be licensed general practitioners) and should have some experience in clinical trials. In practice, most senior physicians would qualify, regardless of whether they are in hospital-based or private practice. Rules for device trials vary slightly in that a "2 year experience in clinical trials" is required of investigators.

The willingness of physicians to participate in clinical research varies considerably and may depend upon incentives. Most potential investigators in major hospitals—particularly university-affiliated institutions—are familiar with and accept

## Documentation required

**Ministry of Health—notification**

- ☐ Completed clinical trial notification form
- ☐ Study protocol
- ☐ Informed consent

**Ethics committee submission**

- ☐ Application form
- ☐ Study protocol
- ☐ Informed consent
- ☐ Clinical investigators brochure
- ☐ Documentation of subjects' insurance coverage
- ☐ Advertising material (where applicable)
- ☐ Case Report Form (requested by some committees only)
- ☐ Investigator curriculum vitae

**Import license for trial medication**

- ☐ Application form (for example, details of number of packages and doses)
- ☐ Trial medication composition (active drug plus ingredients)
- ☐ Address of local distributor or pharmacy authorized to import medicinal products
- ☐ Pro forma invoice

**Drug Advisory Board submission[a,b]**

- ☐ Chemical, pharmaceutical
- ☐ Pharmacological and toxicological
- ☐ Clinical pharmacological (when available)
- ☐ Clinical (when available)
- ☐ Protocol or study outline

*[a] required for a few, select drug trials only; see text*

*[b] report summaries are usually sufficient*

the spirit of GCP. They also know what to expect regarding administrative chores and data quality requirements.

In fact, Austria was one of the first countries to offer formal GCP training to interested physician-investigators. Since 1992, the Board of Physicians has organized a two- to three-week intensive course on the legal, administrative, ethical, and scientific aspects of clinical trials. Courses are offered at regular intervals, and to date a few hundred physicians have participated in this training opportunity.

However, many doctors in smaller hospitals or office practices may lack that valuable knowledge base and positive attitude. Hence, when approaching potential investigators, sponsors should carefully examine those individuals' track records regarding clinical trial experience and formal GCP education.

### Negotiator numbers vary

Formal investigator/site agreements differ between hospital sites and private physicians. Because physician-owned practice groups are still uncommon in Austria, investigators in office practices are usually independent and free to make direct financial arrangements with sponsors or CROs. Most hospitals, however, are community- or state-owned, which introduces a third partner into trial negotiations. A useful, regularly updated desk reference of Austrian hospitals, departments, office practices, scientific organizations and societies is available to help in planning studies.[6]

Unfortunately, attitudes of hospital proprietors/administrators toward clinical trials may be problematic at times. As yet, hospital boards are frequently unaware that trial contracts offer an additional source of income. Rather, the boards view clinical trial contracts somewhat suspiciously—as a likely source of extra cost, with most of the site grant going to investigators. Therefore, except for university-affiliated hospitals where investigators and individual clinical departments enjoy greater autonomy, some hospital administrators offer little help in getting studies started quickly. Sponsors should thoroughly discuss with investigators the level of involvement and the role of hospital administrators in launching a study.

In most cases, however, administrative procedures and rates that hospitals charge will be set and made readily available to interested parties.

### Enrolling subjects

The prevalence of the major diseases in Austria ranks similarly to those of other European or North American communities. Likewise, clinical practice conforms to what one may expect in any other advanced Western nation.

Because of Austria's comprehensive social security system—which covers virtually the entire population—all patients have access to medical care. Yet in the absence of hard data we can assume that, when correlated to population size, the number of clinical trials conducted and the number of patients enrolled at any given time in Austria are considerably lower than those levels in, for example, the United Kingdom, the Netherlands, or Germany. Thus, because enrollment competition remains low, Austria likely has a higher patient base on which to draw for clinical trials subjects.

That is even more true for numbers of healthy subjects because only a handful of centers in Austria conduct healthy-volunteer studies. Hence, the "migration" of professional volunteers that is known to occur with urban-based multiple Phase 1 or basic research units throughout many Western countries is virtually unknown.

Besides disease prevalence, both patient attitude and a willingness to participate in clinical research determine the enrollment capacity of individual centers. Though some segments of the Austrian media are highly critical of clinical research activities, there is no evidence to show that the population at large takes a negative view of clinical trials—or that patients are any less inclined to participate in trials than elsewhere in Europe.

In fact, experience shows that, on average, the patient refusal rate for volunteering for clinical research is low. That may be partly explained by Austria's still highly conservative doctor/patient relationship where patients largely believe that the "doctor knows best." (That belief system applies particularly to the elderly.) Also, most patient populations neither take proactive stances nor assertively seek information.

It is important to understand that, because everyone in Austria is entitled to health care (including drug costs), gaining access to care offers no incentive for patients to participate in clinical trials.

### Finances

Subjects enrolled in nontherapeutic studies in Austria are usually paid for their participation. That includes both healthy volunteers and patients who suffer from disease, such as renally impaired patients who take part in pharmacokinetic trials. No payments are usually made, however, for enrollment in therapeutic trials, except perhaps to reimburse subject for trial-related travel costs or other such expenses.

## SWOT Analysis of Clinical Trials in Austria

**Strengths**
- High standard of clinical medicine
- 100% of patient coverage by social security system
- Rapid initiation of trials possible
- GCP acceptance high among experienced investigators
- Competitive costs compared to many European Union and North American countries
- Availability of experienced CROs

**Weaknesses**
- Lack of investigator/site networks
- Lack of GCP awareness among office practice physicians
- Potential for disagreement among ethics committees
- Low number of patients per site because of high density of hospitals and physicians.

**Opportunities**
- Low level of competition for patients
- High degree of patient willingness to participate in clinical trials
- High availability of healthy volunteers
- Increasing reorientation of physicians toward clinical trials as an additional income source

**Threats**
- Uncooperative hospital administrators
- Hostility of some media representatives to clinical research

Regarding investigator fees, there are no guidelines for freely negotiable investigator grants. Generally, though, fees are somewhat lower than those in northern EU member states. And at university hospitals, charges to sponsors for overhead expenses are very competitive.

### Reporting adverse drug reactions

Against the background of heterogeneous and sometimes confusing adverse drug reaction (ADR) reporting rules in EU member states,[7] regulations in Austria are fairly straightforward. Only serious ADRs require immediate reporting. That can usually be done simply by faxing a completed standardized form to the MOH, the ethics committee at the site where the ADR occurred, and the sponsor.

Reporting rules are similar for device trials, and no report needs to be filed for nonserious ADRs.

### Insurance coverage for subjects

The sponsor holds the legal responsibility for providing adequate insurance to cover all subjects participating in a drug or device trial. Although Austrian law sets no minimal limit for damage compensation, usual amounts range from ATS 5 million to ATS 7 million per patient, which is approximately ECU 450 thousand, or US $550 thousand.[8]

Insurance coverage in Austria must fulfill a number of specific conditions:

- Subjects must be entitled to approach the insurance company directly for claims
- Austrian law must be applicable to all claims
- all disputes that relate to the insurance contract shall be submittable to an Austrian court.

Therefore, for international sponsors that hold blanket contracts with an international insurance provider, it is advisable to involve the Austrian insurance branch at the trial's outset.

### SWOT analysis and conclusion

What are the pros and cons of conducting clinical research in Austria? We have examined that question by studying the strengths, weaknesses, opportunities, and threats—a SWOT analysis— while bearing in mind the needs and interests of non-Austrian sponsors and CROs. Results from our analysis are shown in Figure 2.

Considering the above factors, on balance the timing appears right to start or amplify clinical trial activities in Austria. Yet, though conditions are favorable (thus enabling comparatively rapid and efficient initiation of trials), Austria is still recovering from a reputation as being "difficult terrain." That concept creates a window of opportunity for competitive CROs and sponsoring companies to enter the Austrian market before others inevitably do.

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