

## REPORT

# Ethical and practical issues in conducting clinical trials in psoriasis and psoriatic arthritis

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Ethical considerations are inexorably intertwined with the conduct of clinical research. As a result of progress in immunology and biotechnology, several potent novel therapeutics have recently emerged for the treatment of patients with various immunologically driven systemic inflammatory conditions, including psoriasis and psoriatic arthritis. Because of these developments, there is a need to continually assess the design of current and future research studies so that they may be conducted in the optimal and most ethical manner.

Conduct of clinical research may be the area of medicine most directly linked with ethical considerations. Indeed, many of the milestones in ethical principles have come from deliberations surrounding infamous historical events in clinical research. The intimate association of ethics and clinical research has been well illustrated recently in various autoimmune systemic inflammatory diseases as a result of the introduction of novel, highly effective therapeutic agents. For example, biological agents, in particular inhibitors of the key proinflammatory cytokine—tumour necrosis factor (TNF)—have been shown to be capable of inducing substantial improvements in the signs and symptoms of disease as well as in the quality of life for patients with psoriasis and psoriatic arthritis. The substantial clinical efficacy of these agents has not only spawned further research studies, but it has also raised numerous ethical and practical questions concerning study design in this area, such as:

- Now that these powerful new drugs are available, what are the most appropriate comparators for future studies of other new drugs?
- Under what circumstances, if any, should the use of placebos be permitted?
- What is the responsibility of the sponsor and/or the healthcare payor in continuing to provide expensive therapies to patients after they have participated in clinical studies?

With advancements in basic immunology and in pharmacotherapeutics, ethical concerns have become increasingly complex; it often seems that there are more questions than answers. One approach towards achieving greater insight into these areas is to frame the discussion using several of the core principles of medical ethics. These include patient autonomy, beneficence, non-maleficence, and distributive justice.<sup>1</sup>

## PATIENT AUTONOMY

Many ethicists feel that patient autonomy may be the pre-eminent ethical principle. The tangible expression of patient

autonomy in clinical research is the process of informed consent. There are several key components to adequate informed consent.

Firstly, the patient must have a level of decision making capacity necessary to make a meaningful choice. This includes a patient's ability to understand the information disclosed, appreciate the potential risks and benefits of participation, engage in a reasoning process to include alternatives, and express a choice.

A second and related component of informed consent is that the potential patient must be provided, in language they understand, all the information necessary to make a decision whether or not to participate. This seemingly simple requirement represents one of the most challenging current issues in clinical trials for patients with autoimmune diseases. For example, in the USA, a common guideline is that informed consent documents must be understandable to someone who has completed eight years of primary school education only. However, the science and technology enabling novel therapeutics have become increasingly complex. For psoriasis and psoriatic arthritis, current clinical trials target such diverse components of the immune system as costimulatory molecules, subsets of immunocompetent cells, and inflammatory mediators, using monoclonal antibodies, soluble receptor conjugates, and other novel biological agents. In the future, both the range of targets as well as the treating agents may become even more complex. Providing relevant understandable information to potential study patients will likewise become more challenging. Similarly, the intricacy of adverse events potentially associated with newer therapeutic agents has increased substantially. In the case of TNF inhibitors, there is currently disagreement among experts in the field about the actual risks of these agents as regards certain malignancies, infections, and neurological and cardiovascular sequelae. Therefore, providing accurate information to patients on this topic is complicated. In psoriasis and psoriatic arthritis, the situation is made even more tenuous not only by potential differences in the conditions, which could result in disparate efficacy or safety of a given agent, but also by dissimilarities in the standard of care for these conditions. In the case of methotrexate, for example, dermatologists and rheumatologists have traditionally disagreed in their consideration of the safety of this agent, which has resulted in dissimilar recommendations for optimal dosage, monitoring, and use.

The third key component of informed consent is that it must be given free of coercive influences, which may be subtle. For example, in some countries, TNF inhibitors have not been generally available outside of participation in clinical trials. If patients do not otherwise have access to newer medications, could the potential for receiving them in a research study be considered coercive? If so, does the promise of continued open label therapy with the agent after the study mollify this consideration? Even in countries where newer drugs are available, because of their costs or because of

regulations, access may not be universal. For patients without insurance coverage, clinical trials afford them a means to receive such treatments, which may be a coercive influence to enrol.

### BENEFICENCE

The concept of beneficence is that clinicians will try to accomplish some good for their patients. Of note, this involves a personal good for an individual patient, not just a utilitarian good in terms of benefit to society. A confounder that may affect the clinician's goal of providing good for the patient in clinical trials is potential conflict of interest. Contemporary clinical research has profound economic consequences. More than US\$6 billion per year is spent on clinical trials worldwide. In part, this reflects tremendous scientific advances and the discovery of myriad new therapies. In 2001, more than 80 000 clinical trials involving some 20 million patients were conducted; a threefold increase from a decade earlier. In addition, the process of bringing new drugs to market has become more complex and hence more costly. Currently, it is estimated that more than US\$500 million is spent per drug brought to market. Of course, the financial rewards can be substantial. Sales for two TNF inhibitors, etanercept and infliximab, rose from US\$1.026 billion in 2000 to \$1.565 billion in 2001 and \$1.8 billion in 2002. Financial considerations raise the potential for bias and conflict of interest.<sup>2-4</sup>

A clear example of conflict of interest is where the investigator has a financial stake in the results of the trial. In 1999, Jesse Gelsinger, a patient with a partial enzyme deficiency who underwent gene therapy with an adenovirus died as a result of a reaction to the virus. The principal investigator of the trial owned a 30% equity interest in the company that owned the drug tested, and the university at which the study was performed owned a 3.2% equity interest. Financial considerations may not have affected the investigator's actions during the study, but such incentives present a clear conflict to the ethical conduct of clinical research. Those with equity interests have a defined legal fiduciary responsibility to try to return value to the company, which could be diametrically opposed to the responsibilities an investigator has to a study patient.

Other less blatant conflicts may arise from the financial compensation investigators receive for conducting studies. This may be of even greater concern with the trend towards greater numbers of clinical trials being performed in more diverse settings. In the USA in 1991, 80% of investigators in clinical studies were academic physicians, mostly at large university hospitals. By 1998, this had decreased to 40%, and research studies were being conducted at numerous venues.<sup>3</sup> Performance of studies at academic sites by no means guarantees ethical conduct. There is a symbiotic relationship between the pharmaceutical industry and academic physicians, not only in terms of financial support of departments and in some cases salaries, but also in terms of publications and career investment. The latter raises other considerations, such as bias in presenting data. It has been clearly shown that positive studies are more likely to be published than negative studies.<sup>5-6</sup> Certainly, commercial sponsors have an interest in not publishing negative studies of their products; however, investigators have an obligation to the scientific community to make public data from research trials, even if the trials were unsuccessful.

### NON-MALEFICENCE

Non-maleficence refers to the concept of keeping the patient free from harm. A relevant consideration in clinical trials concerns the use of placebos in studies. Questions on the ethical use of placebos have always generated intense

debate.<sup>7-11</sup> There are certain benefits to the use of placebos in studies. For example, data from placebo controlled studies tend to be more conclusive than active comparator studies, due in part to the potential variability in response seen with many medications.<sup>11</sup> Placebo controlled studies also help define the true extent of response, and they avoid erroneous "therapeutic syllogisms" (drug A is similar to drug B, drug B is similar to drug C, therefore drug A must be similar to drug C) that can suggest clinically irrelevant conclusions. A characteristic of placebo controlled studies attractive to sponsors is that they provide answers more quickly and with smaller numbers than active comparator studies.

The most recent Declaration of Helsinki (revised 2002; available at [www.wma.net](http://www.wma.net)<sup>12</sup>) does not forbid placebos; rather, they are permitted "in studies where no proven prophylactic, diagnostic, or therapeutic method exists". This speaks to the concept of "equipose"; namely, that it is not known before the study whether a new treatment is superior to the comparator. Equipose is central to the ethical design of clinical trials. In psoriasis and psoriatic arthritis, the substantial clinical efficacy of the new TNF inhibitors has raised questions about what is currently acceptable as a comparator for trials. Moreover, the difference in approach to psoriasis and psoriatic arthritis has called into question what the underlying treatment should be for patients entering clinical trials. In rheumatoid arthritis studies, for example, additions of a new treatment to baseline methotrexate and low dose oral corticosteroids is a common study design. In part, this relates to the concern that patients should not be left without any antirheumatic treatment. Also, because methotrexate is the most commonly used antirheumatic drug, this defines an "unmet need" among treated patients. However, because the same is not true for patients with psoriasis, there has been debate concerning the appropriate baseline and comparator therapy for studies in psoriatic arthritis.

The optimal duration of clinical trials is also a matter of debate; the ethical considerations of minimising patient exposure to ineffective or suboptimal agents is often pitted against regulatory demands for longer duration trials to establish specific outcome claims. In psoriatic arthritis, where many patients have synovitis similar to that seen in rheumatoid arthritis, the question arises as to what data may be reasonably extrapolated from the rheumatoid arthritis experience as regards study design in psoriatic arthritis.

### DISTRIBUTIVE JUSTICE

As clinical trials have increasingly become multinational, ethical considerations have been raised not only about the studies but about the treatment of patients after studies have been completed.<sup>13-14</sup> One issue relates to study design. If the standard of care for the treatment of patients with psoriasis or psoriatic arthritis is different in a given country, is it ethical to design a study based on that standard, even if such a study would not be considered ethical in another country with greater resources and a higher standard of care? Another concern relates to continued treatment of patients after a study is complete. The Declaration of Helsinki asserts that, "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified in the study". The efficacy of highly effective agents, such as the TNF inhibitors, raises issues in both those countries where they are available commercially and those countries where they are not. What is the responsibility of the sponsoring company as regards continuing to provide medication to study patients after a study is done but before the agent is commercially available?

## CONCLUSIONS

The considerable excitement surrounding the assessment of novel therapies in clinical trials and their introduction to the clinic in psoriasis and psoriatic arthritis has been accompanied by the realisation that a number of important ethical issues must be considered. Indeed, ethical issues and clinical research have been, and almost certainly will be, inexorably intertwined. Consideration of ethical issues will therefore be critical to the optimal assessment and use of novel therapeutic agents in rheumatology.

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