Clinical Trial in Nephrology at Hard End Point?

DICK DE ZEEUW AND PIETER A. DE GRAEFF
Department of Clinical Pharmacology, University Medical Centre, Groningen, The Netherlands

The clinical trial as it is conceived today has the purpose of evaluating a treatment strategy for a given disease according to a set of more or less strict rules. These rules have been narrowed in the last decade to ensure that the outcome of the trial can be interpreted with success and preferably in only one way. This interpretation should then lead to a new therapeutic strategy for the given disease. Such a treatment strategy is often embraced by the medical community as a standard, and today translated into (part of) a treatment guideline for that specific disease. Thus, we teach our medical students and colleagues that the patient should be treated according to the endorsed guideline, which is based on evidence obtained by a set of fixed rules.

The impact of clinical trials and their outcome are particularly noticed when we are dealing with new treatment strategies involving drugs. Pharmaceutical industries test new compounds in a strict protocolized environment, and regulatory authorities only allow new drugs to enter the market under strict conditions.

In parallel with the higher quality standard, doctor, patient, and society nowadays demand more effective treatment for common and rare diseases leading to increased technology efforts creating high throughput screening for new leads. This subsequently puts a burden on the clinical trialist to come up with more and higher-quality clinical trials.

In this issue of JASN, Strippoli et al. (1) show that there is indeed tremendous growth in the number of randomized clinical trials (RCT) throughout the various disciplines in (internal) medicine. In particular, cardiology shows a near sixfold increase in RCT in the last three decades. They indicate that nephrology also shows growth, but this is clearly less than other specialties. In fact, Strippoli et al. (1) point to the fact that cardiology shows a 10 times higher total number of published clinical trials over the last decades than nephrology. Not only does cardiology do better than nephrology in this regard, according to the analysis of the authors, but nephrology also lags behind compared with all other (internal medicine) specialties. In addition, the authors find that the quality of the published clinical trials (tested by proportions of citations) does rise with time for all specialties; but again, nephrology starts and ends relatively low, although there was an improvement compared with some others. The authors conclude: “Our data on the quantity and quality of trials in nephrology is of major concern and suggest that clinical research in nephrology, and trials in particular, is in crisis.”

Is this really the case? Is it true that clinical trials in nephrology are at an end point as far as quality and quantity are concerned? To judge this, the authors use the classical method of parallel comparison with other disciplines, which is, as the authors indicate themselves fraught with bias by specialization. As all of us in science are well aware, comparing cardiology to nephrology should only be done when we can use it to our advantage; nephrologists would rather forget comparing cardiology with nephrology when it comes to impact factors and citation scores. How do we determine the quality and quantity of nephrology clinical research? To answer that question, we should know the factors that drive the quality and quantity of RCT in general and translate this into the field of nephrology. Some of these factors can be readily identified.

**Type of Specific Area**

Presence and/or rate of occurrence of an untreated or ill-treated disease. The need for better treatment of AIDS has a different meaning and driving force than for treatment of membranous nephropathy. Even within the ten specific areas of nephrology, proportions of RCT can vary to a large extent, as shown by Strippoli et al (1).

**Availability of New (or More) Effective Drugs, Either from the Same Class or a New Class**

The treatment of hypertension shows a new drug class every decade (or more), with many new exponents within this class, while we are still waiting for a new drug class for, e.g., treating minimal change nephrotic syndrome.

**Sufficient Number of Patients Available for a Trial**

Hostetter (2) recently evaluated the difficulties in starting clinical hard–end point trials investigating new drugs on existing therapies. Given the fact that trials on renal disease progression like RENAAL (3) and IDNT (4) needed around 1500 patients, Hostetter argues that future trials with new drugs that improve that therapy strategy will probably require close to 5000 patients. In addition, patient recruitment for adequate quality RCT appears to be particularly difficult in areas like glomerulonephritis and acute renal failure, likely hampered by the fact that these conditions have multiple underlying causes of disease and are relatively scarce.
Funding

The pharmaceutical industry is the source of (co)finance for the clinical (hard–end point) trial in nearly all cases. If the industry does not have a bright future and/or if the drug patent life is not sufficient enough to allow adequate repayment on investments, the intended trial will not be started. Corporate financial incentive is therefore a very important force deciding if and in which area an RCT is conducted. Although there is a lot of evidence that, in addition to BP treatment, progressive renal disease could be halted further by starting to treat other parameters, such as lipid disorders, proteinuria, smoking, and anemia, no hard–end point trials have started yet. However, since there is more financial interest in cardiovascular trials, industry is supporting cardiovascular hard–end point trials on treatment of anemia in diabetes (TREAT) (5) and even on a novel risk marker like C-reactive protein (JUPITER) (6).

Regulatory Requirements

Changes in regulatory requirements such as Medical Ethical Committees, as well as regulatory legislation (European Clinical Trial Directive) (7) can have significant effects on the enthusiasm and options to start a clinical trial.

Capable and Interested Clinical Triallists

Several names continue driving the start of large clinical trials, as these colleagues are the ideal primary investigators for such a task. Without them, no trial will begin or inadequate recruitment may result, and no publication of the results will emerge.

Local Therapy Reimbursement Strategies

In certain countries, trials cannot be conducted because the drug is not allowed on the market or is not reimbursed, which will stop some doctors from enrolling patients in trials.

Many more factors may be present. It is easy to see that the above factors may differ considerably between nephrology and other disciplines like cardiology. This means that the comparison between the two disciplines should be further deepened before drawing the conclusion that clinical trial nephrology is in crisis. Do we have sufficient data to add an analysis based on the above factors to the current analysis of Strippoli et al. (1)? This appears to be very hard, because structured data for many of the above factors is lacking. Although one knows that it will probably have an effect, it is hard to know exactly how it would influence the trial quality and quantity in nephrology.

However, there are some interesting data that may illustrate the importance of using more factors when comparing RCT numbers. Rahman et al. (8) showed that medical clinical research estimated from publications in top journals is particularly productive in the United States, Canada, UK, and the Netherlands. However, if one repeats this analysis for clinical (drug) trials, the UK disappears to 7th place and the United States, Canada, the Netherlands, and France take up the first four places (personal research). Apparently, medical clinical (drug) research is influenced by factors that are country-specific beyond research budget and country size. Should Strippoli et al. (1) have incorporated a country-specific trend in nephrology RCT; if so, would that have altered their conclusion?

A completely different, but maybe more relevant approach to looking at the success of RCT in nephrology would be to evaluate the following questions: How many diseases need (urgent) adequate treatment within a discipline, what type of RCT is being carried out, and how does it contribute in terms of clinical benefit to current guidelines for that disease? In nephrology, one could argue that the need for renal protective treatment was less urgent in the past because renal replacement therapy was present. This was obviously completely different in cardiology where the need for treatment was much more urgent to prevent end-stage heart disease. Clinical trials that test the non-inferiority of one guideline drug versus a new one, as these are currently being carried out in cardiology, usually give us an answer that there is not much more to be expected. Although Strippoli et al. (1) would count this as a clinical trial, the outcome of such a trial may not have any major effect on improvement in patient care. Thus, the best way of comparing RCT between disciplines may be through a test for differences in guideline revenues. An example that nephrology is not doing so bad in this respect, is the fact that both renal (COOPER-ATE) (9) and cardiology trial results (CHARM) (10) have recently been published on the effect of drug addition (angiotensin-converting enzyme (ACE)–inhibitor plus angiotensin II antagonist) on hard outcomes. This in fact would tell us that the renal trial is in the forefront with cardiology, and alive and kicking.

Despite our comments on the analysis, Strippoli et al. (1) have started an important discussion with their initiative. The status of renal patients progressively loosing their kidney function, replaced by a state with poor quality of life, is far from optimal. Many common and orphan diseases in nephrology remain without adequate treatment guidelines. New treatment strategies are needed, and the high quality clinical trial is certainly the way to exploit this further. In addition, the comparison with other disciplines should be used to learn from each other’s ideas. The local country initiatives and the European networks for cardiology research show that multicenter approaches and intense collaborations do work extremely well to conduct quality clinical trials with high speed and efficiency. In nephrology, examples like the Collaborative Study Group (11) and GISEN (12), as well as the collaborations mentioned by the authors (European Vasculitis Group, North American Pediatric Transplant Collaborative Study Group) (1) show that it can also be done in nephrology. We do agree with Strippoli et al. (1) that we need to be much more aggressive in doing this, because many (often unreported) failures to end a multicenter clinical trial in nephrology could have been saved with more concerted structure and action. The nephrology community should bundle their strength to help the growth and structure of these networks. This should be aided by sufficient government funding for such networks (MDRD) (13) because this would boost the number of clinical trials beyond those driven by industry. So, although we may not yet be quite in the crisis mode in nephrology clinical trials, we are hovering just
above it and need to significantly increase our efforts in this important area.

References

See related article, “The Number, Quality, and Coverage of Randomized Controlled Trials in Nephrology,” on pages 411–419.