**Position paper/Perspective**

**Title:** International perspectives on Patient Involvement in Clinical Trials in Nephrology

Authors: Debasish Banerjee1, Racquel Lowe-Jones1, Sandrine Damster2, Nicola Thomas3, Nicole Scholes-Robertson4, Allison Tong4, Adeera Levin5 and ISN-ACT patient-engagement in clinical trials group

Institutions:

1 Renal and Transplantation Unit, St George’s University Hospital NHS Foundation Trust, Molecular and Clinical Sciences Research Institute, St George’s, University of London

2 International Society of Nephrology, Brussels, Belgium

3 School of Health and Social Care, London South Bank University, 103 Borough Road, London, SE1 0AA

4 Sydney School of Public Health, The University of Sydney

5 Department of Medicine, University of British Columbia

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Corresponding address:

Debasish Banerjee

Renal and Transplantation Unit

St George’s Hospital

Blackshaw Road Tooting

London SW17 0QT

Tel +442087251673

Fax +442087252028

email: debasish.banerjee@stgeorges.nhs.uk

The involvement of patients in nephrology clinical trials is limited despite their ability to prioritise research, help with study design, participation and implementation of results. The aim of this position paper is to review the need, challenges and assess the present situation of patient involvement; and describe the role of International Society of Nephrology in promoting patient involvement.

Patient involvement across from priority setting through to implementation of the trial findings can ensure that the evidence generated aligns with their priorities, maximises recruitment and retention, as well as its impact on practice and policy. This has been demonstrated in UK, Australia, Canada and United States, however little is known about the involvement of patients in trials internationally. Barriers to patient involvement includes the patients’ lack of awareness of opportunities to participate, knowledge of clinical research, lack of time, ill health; and lack of initiative amongst researchers to provide opportunity.

To assess patient involvement in clinical trials in kidney disease the International Society of Nephrology surveyed the members of the regional boards to which 177 members responded. The survey demonstrated the variability in patient involvement among different regions, highlighted the lack of nominated leads and formal mechanisms of patient involvement. Though members were keen to communicate with patient, social media was underutilised. The International Society of Nephrology will support patient involvement by developing tools and creating better awareness, to promote high quality clinical trials in Nephrology.

Key Words: Patient involvement, clinical research, clinical trial, nephrology

The need for patient involvement in clinical research

Clinical trials are aimed to generate high-quality evidence about the effectiveness and efficacy of interventions to inform best practices. Traditionally, trials have been led and designed by clinician scientists with very limited involvement of patients. Given the differences in priorities for research between patients and clinicians, trials may not always address the research questions of importance to patients.(1) Also, most of the outcomes reported across trials are clinical, biochemical and surrogate endpoints, while patient-reported outcomes that reflect out patients feel and function are often omitted.(2, 3)

There is a growing body of evidence that patient involvement in clinical research is important in the context of research priority setting, clinical trial design, participation and recruitment, and the dissemination and implementation of results.(4) Patient involvement throughout the process can enhance the quality and relevance of research aimed to improve patient care, and successful implementation of the results.

Recent changes in the prioritisation of research by funding bodies worldwide, reflect recognition of the need to involve patients in the design and execution of research programs. The (National Institute of Health Research) NIHR in UK encourages patients, careers and the public to prioritise research, suggest research topics through online tools, review research applications, join advisory boards take part in the research steering committee, and spread the knowledge as a research ambassador. The Canadian Institute of Health Research provides opportunity for its citizens to be members of the research institute advisory boards to prioritise research, and has launched a Strategy for Patient Oriented Research (SPOR), which encourages involvement of patients in all aspects of research: design, recruitment, interpretation and dissemination (www.cihr.SPOR). The Kidney Patient Involvement Network (KPIN) in the UK is a network of kidney organisations, charities and individuals committed to quality patient and public involvement and engagement who are willing to work collaboratively on initiatives to improve standards and develop patient leaders of the future. The National Health and Medical Research Council in Australia mandates extensive patient and public involvement in grant applications with an aim to make research relevant to community need and translated better to practice ([www.nhmrc.gov.au](http://www.nhmrc.gov.au)) . The Patient-Centred Outcomes Research Institute (PCORI) in the USA in another example to improve patient involvement through research. (see table 1)

The aim of this review is to discuss the importance of patient involvement in clinical trials in nephrology, the existing practices and propose possible ways of improvement in the future and the role of International Society of Nephrology (ISN) to encourage such developments.

Patient involvement in clinical trials in Nephrology

Within nephrology, patient involvement activities can be seen in a few specific areas: UK, Australia, Canada and the US have structured and supported initiatives in which patients have contributed to the research process. The Standardised Outcomes in Nephrology (SONG) initiative is an example of bringing together patients, caregivers and health professionals, in partnership, to establish meaningful outcomes for clinical trials across the spectrum of chronic kidney disease.(3,5) The current scope of work includes haemodialysis, peritoneal dialysis, kidney transplantation, polycystic kidney disease, glomerular disease, and paediatric kidney disease. The initiative has shown a mismatch in priorities for outcomes between patients/caregivers and health professionals. Health professionals consistently give higher priority to mortality and hospitalisation; and patients give higher priority to outcomes that impact on life, such as ability to travel. This reinforces the need for patient involvement to ensure that trials address the impacts of disease and treatment that are important to patients and those involved in their care. CanSOLVE CKD, a Canadian SPOR Chronic Disease network ([www.cansolveckd.ca](http://www.cansolveckd.ca)) engages patients in priority setting, protocol review, dissemination and governance, as well ethics and other infrastructures required for the execution of patient-oriented research in kidney diseases. US-based initiatives, PCORI and KHI, have also involved patients in specific activities related to research activities.

Despite these specific initiatives in the nephrology, little is known about the current state of patient involvement in nephrology from an international perspective. In different countries, regions and continents there are extremes of health care systems, resources and diverse disease patterns, patient demographics and healthcare delivery systems, as well as research infrastructure. Hence barriers to patient involvement are many and different across the globe.

Given the growing importance and focus on patient involvement in clinical research, the growing culture of clinical trials in nephrology, an improved understanding of patient involvement at a local and regional level may informs strategies to the involvement of patients in research..

Challenges to patient involvement in clinical trials

Patient involvement in clinical trials is highly valued by the patient groups, even more so than the academics, as demonstrated in a survey of 179 patients.(6) However, there are significant difficulties for patients to get involved and contribute towards trial design and conduct of research.(7) Patients often are not aware of the opportunity to take part in research design. Some toolkits exist to improve patient awareness but not frequently used.(8)

There are many barriers to patient involvement and include lack of preparation for the role they are going to undertake; practical issues and other issues such as ill-health and culture among groups of patients.

Patients are not often fully prepared for the role they are being asked to do. Researchers do not routinely prepare a role description and often patients are unable to fully understand the scientific background of the study.(9) Some patients may be able to understand the concepts of research design but most patients will have to make an special effort to understand the basics of research before they can contribute.(8) As a result, researchers fail to appreciate the role of patients in study design.(10) Patient education about their role and knowledge and understanding of the scientific rationale for the study is critical in order to facilitate useful contributions.(8) Due to lack of experience, most researchers are unable to deliver the necessary education.

Attending research design meetings may be expensive for patients, as many may not be in full time work, which needs to be addressed to improve patient participation.(8) Even if funds have been allocated for travel and time, patients may be in receipt of benefits which might be affected by additional income. Clear guidance and forward planning may assist patient involvement in research meetings.(9).

 Patients with kidney disease also may not be able to attend meetings, read drafted materials and literature on research proposals due to their illness and fatigue. Lack of experience in research, tiredness due to illness and lack of time, were reported to be major barriers to involvement in research on urinary tract infections by patients in Germany.(9)

Often there are cultural barriers which prevent patient involvement. The involvement and the reporting of it varies between high-income and low/middle income countries.(11) Distance from the study centre in remote rural areas, and language in diverse populations may be barriers which potentially can be overcome better electronic communication and translation services. In a study investigating low recruitment rates among African American women, patients felt health was not their priority and research was only to benefit the privileged.(12). Other anecdotal evidence has shown that the word ‘research’ has negative connotations in some minority groups because of past experiences of unethical experimentation.

A summary of the challenges to patient involvement in clinical trial design is shown in Table 2. These challenges include patient factors, researcher factors and system factors.

In the UK, the Kidney Patient Involvement network (KPIN: https://kpin.org.uk/) undertook a project to examine and benchmark the quality of public and patient involvement (PPI) across the kidney community, using the National Institute for Health Research (NIHR) standards. The standards are focused on inclusive opportunities; working together; support and learning; communications; impact and governance. In 2018 eighty clinicians were asked about what was good and bad about patient involvement during a dialysis conference. In early 2019 a survey based on the NIHR quality standards survey was sent to patients and carers already involved in research (n=30) and asked about their experiences of involvement (across research, quality improvement, projects and committees). From a clinician perspective, their experiences of meaningful PPI included lip service to patient involvement (tokenism), some patients were unwilling, patients were spoken to like children and there was little thought given to expenses for patients’ travel and time. Some patients felt overwhelmed by the requests.

The role of ISN

The vision of the ISN is to have equitable kidney health accessible for all patients worldwide, is predicated on enabling high quality, regionally diverse research and supporting communities to close the gaps in knowledge, policy and care. Thus, the ISN Advancing Clinical Trials (ACT) group was formed to focus on Clinical Research activities.

Since, little is known about the existing infrastructure in the international community about patient involvement in clinical research, and given the growing importance of patient involvement, the ISN-ACT developed a formal plan to explore the existing patient involvement in clinical research in different (ISN) regions throughout the world. With that knowledge, opportunities and barriers could be identified to improve the relevance of trials with patient-important outcome and thereby quality of clinical trials and uptake of trial findings and outcomes in Nephrology.

The ISN survey of its members via the regional boards to understand the existing nature of patient involvement

The ISN commissioned a survey to assess the following:

1. Whether there was any patient involvement in clinical research in the different ISN regions.
2. Whether a patient was already included in the regional board activities. If not, was it possible.
3. Whether the regional board had a nominated patient involvement lead.
4. Whether the regional board had access to patients or a patient group who can help in designing methods and also encourage involvement of patients in clinical trials.
5. Whether the nephrology community in the region had a method of communication with patients. If communication with patient groups was not part of the nephrology community usual work, was there a desire to include them.

Methods of survey

An online survey was developed to determine the level and nature of existing patient involvement in clinical research among the nephrologists in the ten ISN regions. The questionnaire was emailed to the ISN ACT members and distributed through the regional board on 2 occasions, altogether 549 individual members: September October 2018 and November December 2018. The data were analysed using IBM SPSS 25. The introduction to the survey had definitions of Patient involvement, and asked specific questions designed to understand current state, infrastructure and involvement of patients in clinical research in the specific region.

Results of survey

The total number of responses included for analysis was 177, 32% of all members who the questionnaire was emailed to. All ten ISN regions were represented in the responses. The highest number of responders were from South Asia (33%) followed by Oceania and South East Asia (14%) and Latin America and Caribbean (12%). Responders were from 45 different countries with the highest proportion from India (23%).

Characteristics of responders: Mean age of the participants in the survey was 51±12 years. 31% of the respondents were female. 47% of the responders were practicing nephrologists for more than 15 years and 61% were practicing nephrologists for more than 10 years. Only 25 (14%) were trainee nephrologists practicing for less than 5 years. 84% responders were ISN members and 32% were ISN ACT members. 62% worked in University hospitals and another 18% in University affiliated district general hospitals. 26% worked in private hospitals.

Existing patient involvement: 151/177 (85%) responded to the question if there was already patient involvement in the region, and 88 reported existing patient involvement; 37 reported no existing patient involvement, 26 were uncertain and further 26 did not respond to the question. The 3 regions with the highest number positive responses for existing patient involvement were West Europe (71%), Middle East (77%) and North America (62%); the lowest were Latin America, Oceania and South Asia. There was no statistically significant difference between the regional groups (see table 3). There was no difference between males and females.

Nature of existing involvement: 86/177 (49%) responded reported that the involvement was at regional level. The involvement was reported to be for setting research priorities in 49/177 (28%) responses, helping with trial design in 44/177 (25%) and participation in research in 58/177 (33%). There was no statistically significant difference between the regional groups.

Patient involvement in Regional Board activities: Three responders suggested already existing patient participation in the regional board activities, whereas 74/177 (42%) felt it would be possible to have so. 12/177 reported an existing lead member for patient involvement in the regional board and 18/177 (10%) reported that patients were available to the boards for involvement. Some suggested that the regional board have access to patients or patient groups who can help in trial-design and encourage participation in clinical trials. 78/177 (44%) reported that the regional nephrology community have a method of communication with patients; through face-to-face meeting (n=93), workshop (n=44), email (n=32) or Facebook (n=24).

Sensitivity analysis was performed excluding south Asia, given the high proportion of respondents from that region. From the rest, the total number is responses were 118. The mean age was 52±12 years. 39% were females. 65% were practicing nephrologists <10 years. 7% were trainees. 88% were ISN members. South Asians were younger [48±10 vs. 51±12 years, p=0.039] and had less females [9/59 vs 46/118; p=0.001]. 61 participants (52%) reported existing patient involvement. 48 (41%) responded that there was opportunity for patient involvement in the regional board. Hence there was no significant difference between South Asia and other regional boards with respect to existing patient involvement.

Value and limitations of the survey

This is the first assessment to attempt to ascertain the existing nature of patient involvement in renal clinical trials across different regions in the world. Approximately half the participants across all regions reported some patient involvement in clinical research in their region. Participants reported lack of nominated leads and lack of patient access at the regional board level. The survey highlights the absence of formal mechanisms for patient involvement in the regional boards of the ISN. Some communication with patients exists; by means other than social media, in some jurisdictions. However, the survey participants were keen on increasing patient involvement. The response rate was lower in Eastern and Central Europe, North and East Asia, North America and the Caribbean, potentially due to language and other barriers, and thus further work in these regions is warranted. Details of the nature of patient involvement clinical research i.e. in research design, grant review, research delivery, recruitment etc. were not explored in the current survey.

The questionnaire study confirms the variability of patient involvement among the different regional boards and a need for uniform processes to improve patient involvement across all regional boards.

While there is a growing literature to support patient involvement in clinical trials, there are several hurdles to implement standard practices across the world. Systematic reviews suggest the majors barriers are lack of resources, knowledge, training and time. (4) Successful patient involvement requires forward planning by the research team before the study starts, be flexible with time and honour the contributions from patients.

In a recent email survey of 129 clinical trialists involved in 71 surgical clinical trials in UK, similar to the ISN survey 55% responded; and 87% reported involvement of patients (or public). (10) Most of these studies were funded by NIHR and patient involvement was a prerequisite to a successful grant application. When involved the patients (public) helped with study design and were part of the steering committee. The participants of the email survey were unsure about the exact role of patients and expressed different views about their utility and remuneration for their time.

In a UK survey of NIHR funded clinical trials, 21 out of 105 chief investigators responded, of whom 14 described some use of patient involvement while 7 described no benefit at all. (13) They suggested early involvement of patients during design and advisory roles may be more useful; than involving patients late and in non-advisory roles. Not all investigators are convinced of the utility of patient involvement in research. Hence funding bodies need to emphasise the importance. Whereas in an interview majority of 38 patients and public who were involved in a study felt they can contribute towards the research, but not always knew how.(14) With mature patient engagement processes, people can in fact be involved in designing trials, including what is acceptable in terms of number and type of visits. (15)

Patient involvement in the design, recruitment, execution and dissemination of clinical trials, while important, is not yet common in nephrology and in other medical specialties. Among researchers, the understanding of utility and role of patients in research study design and delivery is minimal. We describe that in the international nephrology community, as represented by the ISN regional board members, the awareness is sub-optimal and needs to be prioritised. The findings of the survey suggest that having nominated leads for patient involvement in the regional boards; increasing communication with patients using the nominated leads and utilisation of social media may improve patient involvement in research. Nominated champions, researchers and patients, in the regional boards will improve patient involvement in trials and reporting of such involvement. (16)

Next steps for better understanding the challenges and opportunities of patient involvement in Nephrology Clinical Trials

Developing an international strategy for patient involvement in nephrology clinical research requires improved understanding of the required framework and resources, collaboration with existing successful enterprises, and the adaptation of the methods for local, cultural differences. Better patient involvement in the planning, conduct, and dissemination of clinical trials may help to improve outcomes of patients with kidney disease over time. There is a need to educate clinicians, trialists, policy makes and patients as to the value of this, and establish the appropriate structures to ensure sustainability of the efforts.

ISN future plans for improving patient involvement in clinical research

With accumulating data that there is value to including patients in all aspects of research, and recognizing the diversity in perspectives across the globe, ISN has committed to enabling and improving patient involvement.

International Society of Nephrology – Advancing Clinical Trials (ISN-ACT) aims to develop frameworks and tools which promote high quality, patient orientated clinical trials in Nephrology across the globe. In this facilitative role, collation of ‘best practices’, in various aspects of clinical trials, derived from all regions is important. The remit of the “Patient Engagement ” working group is to encourage more meaningful involvement of patients from study design to implementation; starting with an increase in awareness of current activities in different regions. It is clear from the survey that there are significant differences in patient involvement in clinical trials, within and across regions. Some regions have been able to encourage patients to actively participate in trials, others are still finding ways to do so. There are several challenges in patient involvement which may be related to poor research infrastructure, lack of awareness among researchers, lack of understanding of patient priorities and the disease burden of patients. Differences in healthcare delivery and cultural differences also play a role. There is increasing interest from regulators, funders (public and industry), research organizations and trialists to include patients in trial design. Thus the ISN effort to promote and facilitate patient engagement fits well with this new direction. Thus, future work will involve promoting awareness, and developing tools and platforms for interaction, which can be accessed worldwide.

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**Tables**

Table 1: Web-based resources on patient involvement in clinical trials

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| --- |
| Available resources to improve patient involvement in clinical research |
| <https://songinitiative.org/>  |
| <https://www.nihr.ac.uk/patients-carers-and-the-public/>  |
| <http://www.cihr-irsc.gc.ca/e/41592.html>  |
| <https://www.pcori.org/>  |
| <https://www.nhmrc.gov.au/about-us/publications/statement-consumer-and-community-involvement-health-and-medical-research>  |
| <https://www.nih.gov/health-information/nih-clinical-research-trials-you><https://kpin.org.uk/><https://www.invo.org.uk/>  |

Table 2: Challenges to patient involvement in clinical trial design

|  |  |  |
| --- | --- | --- |
| PATIENT FACTORS | RESEARCHER FACTORS | SYSTEM FACTORS |
| Lack of awareness about how to get involved | Lack of knowledge about how to undertake meaningful involvement | Lack of systems/methods for advertising PPI opportunities  |
| Are not given full information about what is required (PPI role description) | Perception that PPI is too resource intensive (time and money) | Lack of funding to reimburse people with lived experience for their time and expenses |
| Are not prepared well enough for the role  | Do not see the worth and impact of PPI | Payment for PPI can be complex, especially if patients are in receipt of benefits |
| Research meetings are not scheduled according to patient need (eg. dialysis day, accessibility of meeting venue) | Do not understand how to recruit people to PPI groups | Resources to encourage PPI are not known and/or not widely used |
| Are not given feedback on the study results or their contribution | Do not understand the range of possibilities to involve patients in study design, as the perception is that RCTs/basic science are ‘too difficult’ for patients to understand  |  |
| Do not feel valued, especially when involvement is perceived as ‘tokenistic’ |  |  |

Table 3: Existing Patient Engagement by ISN region

|  |  |  |
| --- | --- | --- |
|  | **Existing Patient Engagement** | Total |
| Yes | No | Uncertain | Yes (%) |
| ISN Region | Africa | 2 | 3 | 3 | 9 (53%) | 17 |
| Eastern and Central Europe | 0 | 1 | 1 | 2 (50%) | 4 |
| Latin America and the Caribbean | 2 | 10 | 2 | 8 (36%) | 22 |
| Middle East | 0 | 1 | 1 | 7 (77%) | 9 |
| NIS and Russia | 3 | 2 | 2 | 7 (50%) | 14 |
| North America and the Caribbean | 1 | 1 | 1 | 5 (62%) | 8 |
| North and East Asia | 1 | 1 | 0 | 3 (60%) | 5 |
| Oceania and South East Asia | 3 | 6 | 6 | 10 (40%) | 25 |
| South Asia | 12 | 11 | 9 | 27 (46%) | 59 |
| Western Europe | 2 | 1 | 1 | 10 (71%) | 14 |
| Total | 26 | 37 | 26 | 88 (50%) | 177 |

Table 4: Key messages

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| --- |
| Key messages |
| Patient involvement in clinical research will improve utility of the results |
| Patients should be involved at all stages of research including design, delivery, dissemination , implementation and translation |
| Considerable challenges exist for meaningful patient involvement |
| Country and region-specific patient involvement is important  |
| The patient involvement in nephrology clinical trials in different ISN regions is variable  |
| Most ISN regional boards do not have a nominated patient lead, which may be beneficial |
| Most ISN regional boards do not have access to patients (or public), however would like access to patients |
| ISN regional boards communicate with patients face to face, use of social media may help with recruitment |