

Archiving Pakistan Society of Nephrology Research Taskforce (2022-2024) 18 Month Initiatives to Advance Clinical Research Within Pakistan

K. H. Mujtaba Quadri¹, Waqar Kazmi², Beena Salman³, Rubina Naqvi⁴, Shoukat Memon⁵, Ali Asghar Lanewala⁴, Farrukh Koraishy⁶, Ruquiya Qureishi³, Salman Imtiaz⁵ (All equal first authors)

¹Maroof International Hospital, Islamabad, Pakistan.

²Karachi Medical and Dental College, Karachi, Pakistan.

³The Kidney Center, Karachi, Pakistan.

⁴Sind Institute of Urology and Transplantation, Karachi, Pakistan.

⁵The Indus Hospital and Health Network, Karachi, Pakistan.

⁶Stony Brook University Hospital, New York, USA.

Corresponding Author

KH Mujtba Quadri

Maroof International Hospital

Islamabad, Pakistan

mujtaba.quadri@maroof.com.pk

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The PSN Research taskforce Journey through PAKISTAN



Introduction

The key barriers to globalization of clinical research were identified by Glickman and colleagues viz. absence of and therefore a need for capacity building to perform high quality clinical research in developing countries.¹ This includes efforts directed at clinicians, Pharmacists, Nurses, Biostatisticians and Clinical research associates. Additionally, there is a perceived need for a greater

awareness of ethical aspects and obligation to protect vulnerable research subjects to ensure adherence to Belmont principles of autonomy, beneficence and justice.²

Researchers affiliated with the Pakistan Society of Nephrology, in majority of the institutions within Pakistan, over the past few decades have been involved in varying degrees of inconsistent clinical research efforts fraught with validity issues. These studies have centered around mostly descriptive studies, retrospective observational studies (case -control) and cross -sectional studies. There have been minimal cohort studies, very few randomized controlled trials albeit with methodological limitations and rarely performed systematic reviews and meta-analyses as shown in Table 1.³ The latter two occupy the apex of the evidence pyramid where Pakistan has lagged behind in terms of international representation both vis- a -vis presentations at international conferences as well as published manuscripts within reputable journals.⁴

Using the search terms “Kidney” OR “Renal” OR Nephrology ANDSR/RCT/Cohort/Case-Control/Cross Sectional study and Pakistan in Feb 2022 by Author 1, revealed the following sobering results in PubMed and the locally popular PakMedinet database, even in terms of quantity.

When using Google Scholar, the following search terms were used: Kidney OR Renal OR Nephrology and chronic kidney disease/Nephritis AND Pakistan. The results are depicted in Table-1

Table 1: Number and Type of publications from Pakistan when searched in the database of Pubmed, Pakmedinet and Google scholar.

Pub Med	RCT 2	SR 0	Cohort 2	Case Control 1	Cross Sectional 15
PakMedinet	RCT 0	SR 0	Cohort/Case-Control/Cross Sectional 42		
Google Scholar	RCT 16	SR 1	Cohort/Case-control/Cross sectional 1042		

A Pakistan Renal Data System (PKRDS) registry ongoing for over 3 years for dialysis patients with Metrics CRO is a commendable attempt to collaborate nationally.⁵ However, this is not a solution obviously if we are to improve our nephrology practice and policies through locally generated and internationally benchmarked translational research evidence.

Therefore, to address this perceived gap in capacity to perform high quality kidney disease research in Pakistan, author 1, highlighted the urgency of this issue at the PSN 13th biennial meeting in March 2022 at Quetta, in a presentation entitled “State of Renal Research in Pakistan” .³

It was emphasized that “the Pakistan Society of Nephrology and the Nephrology community, has the challenge and opportunity to transform ourselves with a step wise program of translational research in order to generate valid local and internationally benchmarked evidence” .

“Our research endeavors should be patient-centered, relevant, cost effective and targeted to improving general and renal health outcomes” .

“Research infrastructure, capacity building and mentorship programs need a buy-in of all stakeholders (supervisors, practicing Nephrologists and all trainees)” .

Additionally, “Multidisciplinary teams working collaboratively can be developed in a proposed collaborative North 1, North 2 and South 1, South 2 Pakistan Kidney Research Network.

It was stressed that “Research needs to be incentivized through central grants/ R and D funds and endowments” . It was further proposed that Pakistani origin clinical and translational researchers within academic faculties in US, UK, Australia/ NZ and the Middle East can serve as research advisors/mentors and collaborators in the not distant future. The presentation concluded thus: “Translational research is in essence the equivalent of creation of ‘Ilman Nafian’ , (beneficial knowledge), a legacy of pioneering giants in our own traditions such as Ibn-e-Sina and modern giants” ⁶ .

At the conclusion of PSN Quetta, 2022, a letter to PSN President in April 2022 was formulated highlighting the need to address the gap in high quality translational research in Pakistan. This was taken not only positively but with all the requisite seriousness. Subsequently the PSN Executive committee through a series of meetings endorsed the formation of several PSN Taskforces in October 2022, under an Advisory Committee to be chaired by (late) Prof Tahir Shafi. These included Advocacy and awareness, Academics, Research and Clinical Task Forces (CKD, AKI, GN, PD, HD, Transplant)

Research Taskforce (Terms of reference):

The Research Taskforce was entrusted to contribute to National efforts in capacity building for both faculty, trainees and allied professionals. It was expected to review any submitted research proposals and provide feedback on ethical and methodological aspects. The steps to ensure formation of Institutional review boards and Clinical research units were to be facilitated where requested. Facilitating securing international grants and collaborative trials was encouraged. A collaborative multicenter trial network was to be established with appropriate registration. Finally, it was requested to help strengthen the quality of submissions to the Pakistan Journal of Kidney Diseases.⁷

The need to consolidate, replicate and learn from this subsequent coordinated and collaborative National effort and to archive it for posterity, informs this special communication.

Methods

The taskforce set about its mission with an onsite and zoom based hybrid meeting of all taskforce members on Nov 26, 2022 at PSN President secretariat 2022-2024, SIUT, Karachi. It was felt that all aspects of the terms of reference could be addressed by focusing all our efforts Nationally around capacity building. This was strategized as the key initiative for our inaugural years as a taskforce. A series of taskforce meetings, workshops, Journal clubs and research education efforts were planned.

Capacity building program:

A program of four to six weekly Research fora meetings commenced from Dec 2022 and continued through till Jan 2024. Submissions of proposals or queries were solicited.

Five blended two days research capacity building workshops beginning in February 2023, from Shaikh Zayed Post Graduate Medical Institute, Lahore and ending in August 2023 at Quaid-e-Azam International Hospital, Islamabad, were interspersed with workshops in Peshawar at Khyber Teaching hospital, followed by the Indus Hospital Karachi and Baluchistan Institute of Nephrology and Urology, Quetta.

Nearly 200 faculty members, Nephrology fellows, Residents and allied Clinical research professionals were trained onsite and nearly 50 also registered via zoom based distance learning. Our facilitators were senior Nephrology Faculty members, who had additional qualifications inclusive of PhD in Translational Data Science, Masters in Epidemiology and Public Health, Masters

in Bioethics and Certification in Principles and practice of Clinical research. We also had a dedicated Biostatistician in the shape of a physician with Masters in Epidemiology and Biostatistics.

The themes addressed in these workshops under a select group of 7-9 faculty members (the authors) as facilitators and coordinators included: Research Ethics, Informed consent, Good clinical practice, Formulating a research question, Types of study designs including detailed interactive sessions on Observational studies (Cohort, Case control, Cross Sectional designs), Randomized controlled trials, Systematic reviews and Meta analyses. Additional sessions were on proposal writing, grant writing/budgeting, synopsis and manuscript writing.

Day 2 hands-on workshops were on descriptive statistics, inferential statistics, sample size calculation, SPSS 1 and 2 workshops with data sets imputation, cross - tabulation and generation of statistical outputs. The reading materials distributed to workshop participants included a set of 25 reference articles with details of clinical research ethics and methodologies inclusive of the CONSORT, STROBE and PRISMA statements. The NIH "Introduction to principles and practice of clinical research" textbook was recommended as the course reference text. Additional material distributed included the Comstech Handbook of Randomized Controlled trials.⁸

An interactive quiz at the end of each of the workshops served as an informal method of assessing whether learning objectives were being met. The workshops were all free for registered participants, sponsored by PSN allied industry and faculty voluntarily offered their time, services and efforts gratis.

Additionally, monthly Journal clubs which were merged with Research for a subsequently, commenced in Jan 2023 rotating amongst various centers of the country and predominantly in the provincial and federal capitals as coordinating centers. The articles were distributed ahead of time and presented via zoom based sessions by faculty and critically appraised under designated National mentors. These included Randomized controlled trials, Systematic reviews and Meta Analyses as well as Cohort and case- control studies. All aspects taught and learnt through the workshops were revisited in detail during these critically appraised Journal club presentations. On an average 20-25 participants were present during most of these Journal Clubs. These journal clubs have been distributed now to over twenty teaching institutes and are being presented by Nephrology trainees, along with a supervising faculty member and national mentors.

Subsequently in August 2023, at the suggestion of one of the taskforce members in early 2023, three collaborative National research groups were formulated from within the taskforce. Participants interested in collaborative research were invited and transported to Islamabad for a first ever dedicated Research focused National conference and workshop on Aug 14, 2023. Seven proposals were received nationwide and three were shortlisted for small group discussions. All workshop participants were given worksheets with CONSORT and STROBE statements and were encouraged to formulate the research hypothesis and question and propose eligibility criteria with study design and outcome measures. See Figure 1 below.

Subsequently each of the three collaborative groups worked collectively to consolidate their research proposals over the next three months, obtain their respective IRB approvals and register as required with Drug Regulatory Authority of Pakistan and National Bioethics committee. One proposal was aborted because of a perceived feasibility issue and two were finalized. This includes a Randomized controlled trial being initiated by a Taskforce faculty member (author) at SIUT and a National CKD Registry that was initiated by a Taskforce member from the Indus Hospital Karachi. A dedicated

CRO, Metrics has been initially assigned to facilitate these projects and in continuity of their role in establishing PKRDS registry of dialysis patients in Pakistan.



PAKISTAN SOCIETY OF NEPHROLOGY RESEARCH WORKING GROUP Meeting Agenda

- A. Formulate Research Question
 - B. Proposed study design (RCT /Cohort/Retrospective cohort)
 - C. Developing Primary and Secondary outcome measures
 - D. Eligibility: Inclusion and exclusion criteria
 - E. Sites: Assign responsibilities for portions of proposal as per STROBE or CONSORT guidelines F) PI and Co PIs:
 - F. PSN Seed grants for each group/ center
 - G. Authorship as per ICMJE criteria (ideation, design, methodology, data analysis PLUS write the first draft with each author contribution PLUS write the revised draft with each author contributing PLUS take public responsibility for content
 - H. NB: Authorship may be according to weighted contribution, equal or alphabetical order
 - I. Agree on Timelines:
- Oct 1 Finalize proposal via weekly or fortnightly Zoom mtgs or on Whatsapp group
- Oct 2- Oct 31: Deadline to obtain IRB approval at participating sites
- Nov 1- Nov 15 Recruit Research Assistants and commence research projects
Duration: 1 to 2 years as feasible
- 12:30- 1:00 PM** Seven (7) Minute summaries by Gp 1, 2, 3 and 4 representatives on Powerpoint
- 1:15 -1:30 PM** Zuhr prayer
- 1:30- 2:15 PM** Lunch and conclusion Proposed: **Prof K H Mujtaba Quadri and Prof Waqar Kazmi** Co Chairs PSN Research Taskforce 2022- 2024

Figure 1: Pakistan Society of Nephrology research working group meeting agenda held on 14 August, 2023.

By December 2023, the Research Taskforce was merged into a Research committee with a broad National representation and 3 year term and tasked with consolidation and building up on this colossal national effort to advance translational renal research in Pakistan. Figure 2 below summarizes the Terms of reference but in essence, this document suggests a consolidation of efforts through ongoing capacity building, networking, collaborative studies and dissemination of research output, in addition to seeking international opportunities.

The PSN Executive committee has subsequently formulated a process for multicenter studies in Pakistan. See Fig 3 below.

Results

All workshops to date sought participant feedback but in Khyber Teaching Hospital Peshawar, most of the registrants were trainees in Nephrology which is what is depicted in Figure 4 below.

Collaborations

On an international level, efforts are underway to collaborate with Pakistani diaspora in North America, inclusive of APPNA Merit Research committee to help bring in multicenter clinical trials into Pakistan. One such initiative included sharing of list of current Phase II and Phase III Renal Clinical trials worldwide report provided by APPNA Merit Research Chair, 2024 with the PSN as

well as with our allied CRO. One of the Renal Translational scientists of Pakistan origin, from USA (one of the authors) has already played a key facilitative role in both the capacity building efforts, as well as with the registry initiatives and trained participants in best practices in proposal and grant writing. Figure 5 summarizes the program evaluation to help future planning at the National and International level by the newly appointed Research committee, with a fresh induction of research leadership envisaged and recommended.

TERM OF REFERENCE FOR PSN RESEARCH COMMITTEE (PSNRC)	
DEFINITIONS:	
ABBREVIATIONS:	
PSN:	Pakistan society of nephrology
PSNRC:	Pakistan Society of Nephrology Research Committee
CRO/SMO:	Contract research organization, Site Management organization
PJKD:	Pakistan journal of kidney diseases
RCT:	Randomized controlled trial
TORs:	Terms of Reference
1. FORUM MANDATE:	
	The purpose of this committee is to facilitate and help stream clinical data with the CRO/SMO. The committee will also take all measures to protect data and to review the research projects by contributing hospitals and personnel.
2. MEMBERSHIP:	
	The PSNRC will comprise the following 11 members:
2.1.	Chair PSNRC
2.2.	Deputy chair
2.3.	Secretary PSNRC
2.4.	Representatives from all four provinces and Islamabad
2.5.	The selection of members will be as follows: 3 from Punjab (1 from the south, 1 from the north, and 1 from the center) 2 from Sind (1 from Karachi and 1 from the interior) 1 from KPK, and 1 from Baluchistan
2.6.	Representative CRO/SMO
2.7.	Representative from the PSN Executive Committee
3. CHAIR/ DEPUTY CHAIR:	
	The chair of the Committee will be an elected PSN member, selected/elected by PSN ECC
4. SECRETARY:	
	A representative from PSN ECC will be the secretary of the Committee. He / She will be responsible for scheduling meetings and taking the minutes.
5. TENURE AND REAPPOINTMENT OF CHAIRS AND MEMBERS:	
	The tenure of membership for the faculty shall be three (3) years. They may be reappointed for another consecutive term, the continuation of membership not exceeding two (2) terms consecutively. They can be reappointed after a gap of one term. The tenure for other members would last the duration of the appointment under a specific designation.
6. MEETING SCHEDULE:	
	The PSNRC will meet quarterly or as decided by the Committee Chair.
7. PARTICIPATION:	
	The quorum for a meeting is set at 50% attendance of the members.
8. METHOD OF DECISION MAKING:	
	Decision-making will be by consensus.
9. REPORTING RELATIONSHIP:	
	The PSNRC will report its activities and outcomes to the President through sending regular minutes.
10. CORE FUNCTIONS/DELIVERABLES:	
10.1.	To maintain harmony among participating centers and to set minimal annual research targets for each hospital as well as maintaining a central log of all published research through its secretary.
10.2.	To develop the capacity to execute RCT and cohort studies by PSN itself and develop a team at the national level in participating hospitals.
10.3.	To increase the scope of renal research in Pakistan and to collaborate with other national and international studies and trials.
10.4.	To develop research Guidance for researchers and work out for generating funds for research
10.5.	To present a quarterly report to the PSN President
10.6.	To issue data on important findings to awareness and adequacy task force for dissemination on different public social media and on the website.
10.7.	To publish its quarterly report to PJKD
11.	The procedure/flow of applying for any study by a researcher through PSNRC is mentioned in Figure 1
12. RESPONSIBILITY:	PSNRC Committee
13. RIGHTS OF ACCESS:	PSN President and general secretary and Chair and secretary PSNRC

Figure 2: Summary of the terms of reference for PSN research proposal committee.

Discussion:

A major step was undertaken to advance translational renal research in Pakistan over the past 18 months period. These efforts required investment of time, efforts, human and financial capital. The Pakistan Society of Nephrology is indebted to our dedicated team.

What is proposed now is that capacity building workshops continue to be offered twice a year, in different cities in rotation, six months apart. The Journal Clubs on a monthly basis with Nephrology trainee participation will help Fellows learn the ropes of clinical research with valid internal and external validity and which will help subsequently generate higher order translational research evidence. CPSP may want to consider moving to a model where Fellows participate in ongoing high quality clinical studies and contribute towards manuscript writing both with interim and finalized results. Research needs to be incentivized in the form of dedicated Research months in each year of Fellowship progressively increasing in number e.g. one, three and five months in each subsequent year of Fellowship training respectively. Research grants need to be announced by the new Research committee leadership with defined timelines and with annual review and anticipated mandatory dissemination of interim or final results at biennial PSN meetings and other platforms.

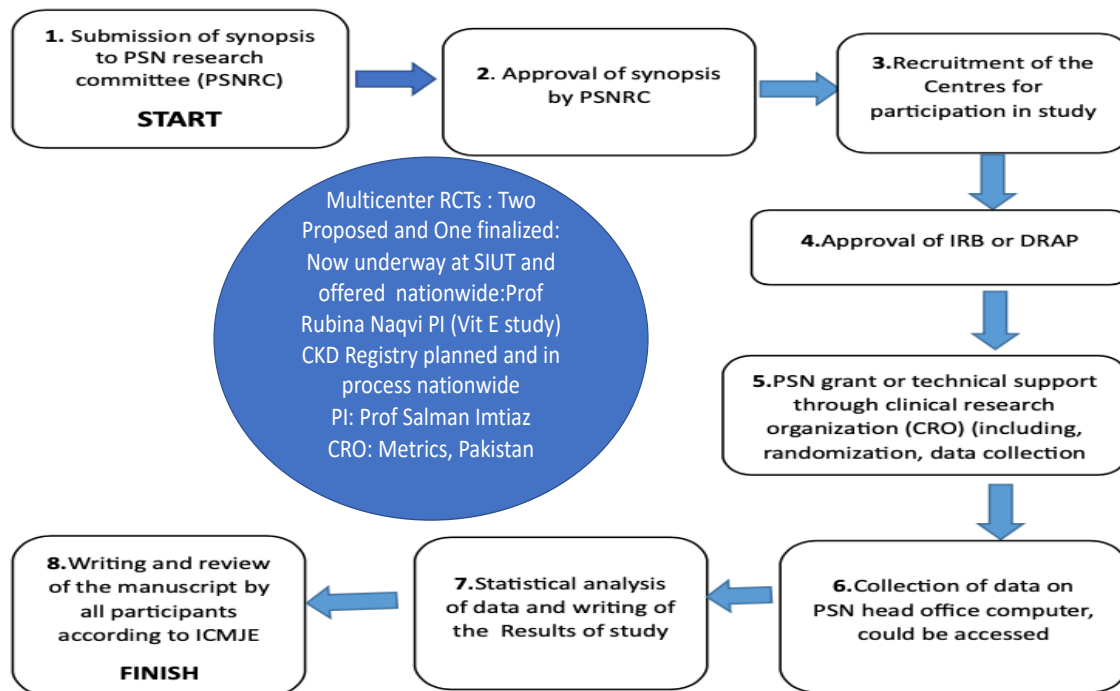
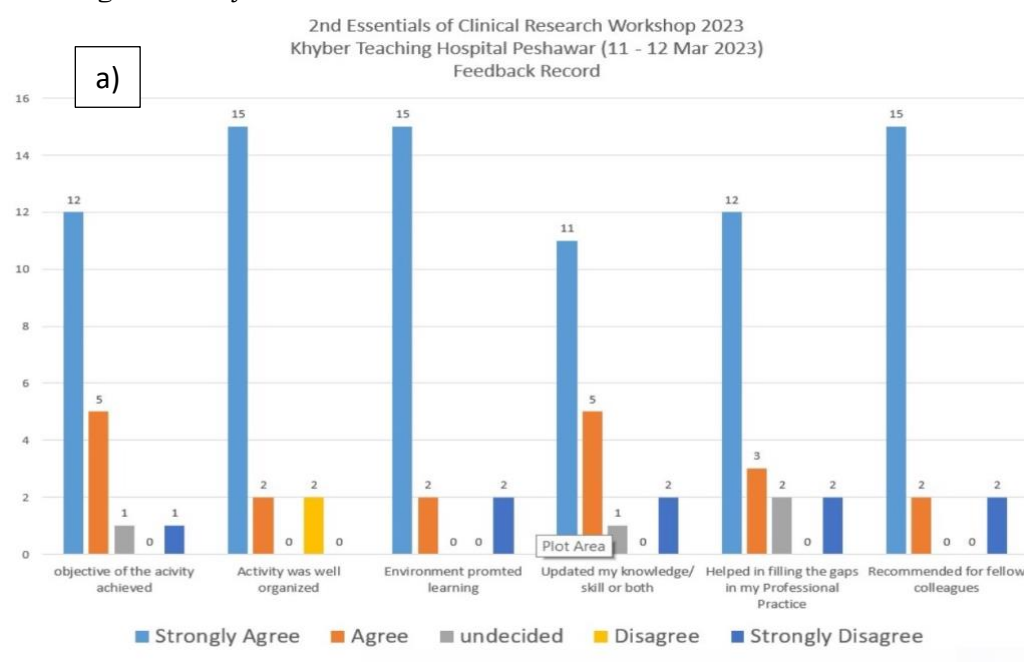


Figure 3: Process of applying for multicenter clinical study by Pakistan Society of nephrology.

The National mentors are requested to continue to support these activities and earn the gratitude of both the Pakistan Society of Nephrology and the Nephrology community, but also the nation at large. With nearly 250 members of the Nephrology community in Pakistan trained in best research practices coupled with ongoing research education efforts, Pakistan is now positioned to undertake collaborative National studies and generate Level one locally relevant, research evidence to inform both our practices as well as policies. In addition, we should now be able to attract International academic and industry -sponsored Nephrology trials after securing Drug Regulatory Authority of Pakistan, site license and widely available, mandated Good Clinical Practice certification (e.g. NIH NIDA, USA).^{9,10} Thus, we would be able to compete internationally to help contribute towards a knowledge economy.



b)

Additional Participant feedback

the activity has brought a change in my:	Yes	No	No Answer	Remarks
Competence	15	2	2	1. Clinical Research 2. Improve Synopsis & dissertation writing skill 3. Improved understanding good Clinical Practices 4. Gave us idea about conducting Clinical Trial 5. I was so weak in writing synopsis and article, this workshop has improved my ability to write and work on clinical research
Performance	14	3	2	1. It was good Activity but time was short 2. Improved understanding of Synopsis writing 3. To perform relevant workshop for study Design 4. will definitely write papers and will participate in research studies
Patient Outcome	9	6	4	1. Improved Ethical understanding when considering patient care 2. for safety care of patients

Figure 4: a) Participant feedback from our second “Essentials of Clinical Research” workshop in KTH, Peshawar.
b) Additional comments by participants

We suggest, this is a shared National responsibility and we need to further consolidate and translate this research effort, to a progressively higher level, in order to consolidate the gains. figure 6 below summarizes the proposed way forward.

Program evaluation: PSN Research Taskforce Nov 2022-Feb 2024

- Five hands-on two day Research workshops conducted in 4 provincial capitals and in capital
- Nearly 200 workshop participants onsite and 50 on zoom trained
- Over 10 Monthly mentored J Clubs conducted with RCTS, Cohort studies & Systematic Reviews
- Over 10 Taskforce minuted meetings and Research Fora conducted
- 1 National collaborative proposal development workshop conducted for 60 faculty members
- 7 proposals for collaborative research received
- 4 proposals discussed in three working groups over 3 months and two bore fruition (IRB approvals)
- 1 National collaborative RCT and one CKD collaborative Registry underway
- CRO : Metrics appointed as liaison for above
- Proposal for PSN Research committee approved in Dec 2023 with a 3 year term and amalgamation and dissolution of PSN Research Taskforce
- APPNA MERIT Research liaison established with exploratory potential for International Trials
- PJKD : Indirect contributions through capacity building, with anticipated improvement in clinical research quality
- PSN Biennial meeting 2024 : National speakers with original national data selected for invited talks

Figure 5: Summary of the program evaluation to help future planning at the National and International level by the newly appointed Research committee

Where there is a will there is a way” (George Herbert)

PROPOSED WAY FORWARD: NATIONAL PROJECTS

- PKR SEED GRANTS BEING GENERATED BY PSN
- PSN RESEARCH ENDOWMENT FUNDS TO BE CREATED IN PARALLEL
- FIVE CATEGORIES OF GRANTS TO BE ANNOUNCED BY May 1, 2024
- DEADLINES FOR SUBMISSION : MAY 31, 2024
- FINAL DECISION BY PSN RESEARCH AND GRANTS COMMITTEE JUNE 21, 2024
- IRB APPROVALS AND DRAP IF REQUIRED : JULY 21, 2024
- PROJECT DURATION : ONE TO TWO YEARS ON RENEWABLE BASIS
- FINAL OR INTERIM REPORTS MANDATED AT PSN MARCH 2026 and repeat cycle
- ONGOING MENTORED MONTHLY JOURNAL CLUBS AND RESEARCH FORA
- TWO ANNUAL RESEARCH WORKSHOPS : NORTH AND SOUTH IN ROTATION
- PAKISTAN JOURNAL OF KIDNEY DISEASE AND INTERNATIONAL PUBLICATIONS
- YOUNGER RESEARCH CHAIRS AS LEADERS WITH NATIONAL Mentors/Advisors

Figure 6: Proposal of way forward by the PSN research Task Force.

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