

HOPE FOR CURE

QUARTERLY BULLETIN FOCUSING RARE DISEASES IN SRI LANKA

HOPE FOR CURE

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Successful execution of clinical trials in Sri Lanka during COVID-19 pandemic

Clinical trial conduct in Sri Lanka was impacted by COVID-19 pandemic.

The COVID-19 pandemic had an impact on our ongoing trials, the opening of new trial sites in existing trials, the ongoing recruitment of participants in trials, as well as the commencement of new trials.

There were a number of difficulties, which led to limitations on visits to healthcare facilities, an increase in the demand for health services, and adjustments to the availability of trial staff. In certain instances, trial participants had to self-isolate as well, which made it challenging for investigators to continue their medical supervision. The completion of trial assessments, the completion of trial visits, and the administration of investigational medical goods were all impacted by these difficulties.

We have, however, been able to successfully overcome these challenges. The decisions were made based on benefit-risk analyses, contingency plans, and prioritizing the effect on the trial participant's health and safety. When a trial participant was unable to visit the site, home nursing, phone communication, or telemedicine were used to track adverse events and guarantee ongoing medical treatment and supervision. Although there are risks and restrictions, we can nevertheless maintain data protection.

Through this, we could successfully meet the needs of the experiment while guaranteeing and prioritizing the overall wellbeing and best interests of the trial participants.



Message from Director/CEO



Samantha Ranatunga
Director/Chief Executive Officer

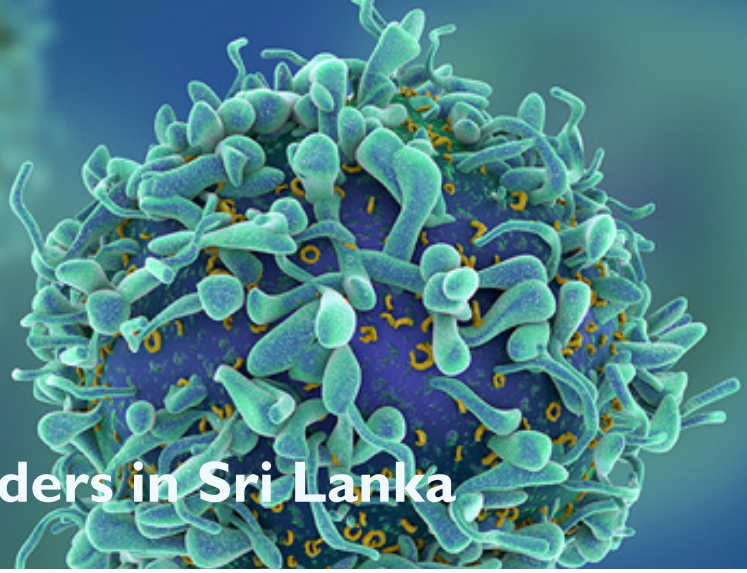
Dear Partner,

In our journey of constant improvement, the quarterly rare diseases bulletin is another milestone. It is to highlight the intended focus rare diseases have within our clinical community.

As our partners, we hope that the message is carried through and Sri Lanka and the region gets focus in this area.

The bulletin also provides an opportunity to our young scientific staff to enhance their talents and skills as well and to learn more about clinical conditions.

We seek your support in this endeavor.



Rare Oncological Disorders in Sri Lanka

Disease Burden

- According to latest Global Cancer (GLOBOCON) estimates for Sri Lanka, 23,530 new cases and 14,013 deaths occurred due to cancer in year 2018 [3].
- The incidence and death rate are expected to increase by 23% every year till 2030.
- Cancer has become the second commonest cause of hospital mortality in Sri Lanka by constituting 14% of all hospital deaths [2].
- As per literature the commonest cancers reported in Sri Lanka are
 - Biliary Tract Cancer
 - Multiple Myeloma
 - Glioblastoma
 - Mesothelioma

Rare Oncological Diseases in Sri Lanka		
Disease	Epidemiology data	Local Standard of Care
Biliary Tract Cancer	2 patients per 100 000 population [2]	Radiotherapy, Adjuvant therapy, Neoadjuvant therapy;
Multiple Myeloma	2.1 patients per 100,000 population [3]	Targeted Therapy, Surgery, Immunomodulators, Corticosteroids, Radiotherapy
Glioblastoma	incidence of less than 10 per 100,000 people [4]	Temozolomide, Bevacizumab, Cisplatin , Radiation therapy, Surgery
Mesothelioma	those with incidence <6/100,000 per year [5]	Surgery, Radiation therapy, Chemotherapy, Immunotherapy

Disease registry is available.

NCI (National Cancer Institute) and specialty cancer treatment centers see a greater number of patients

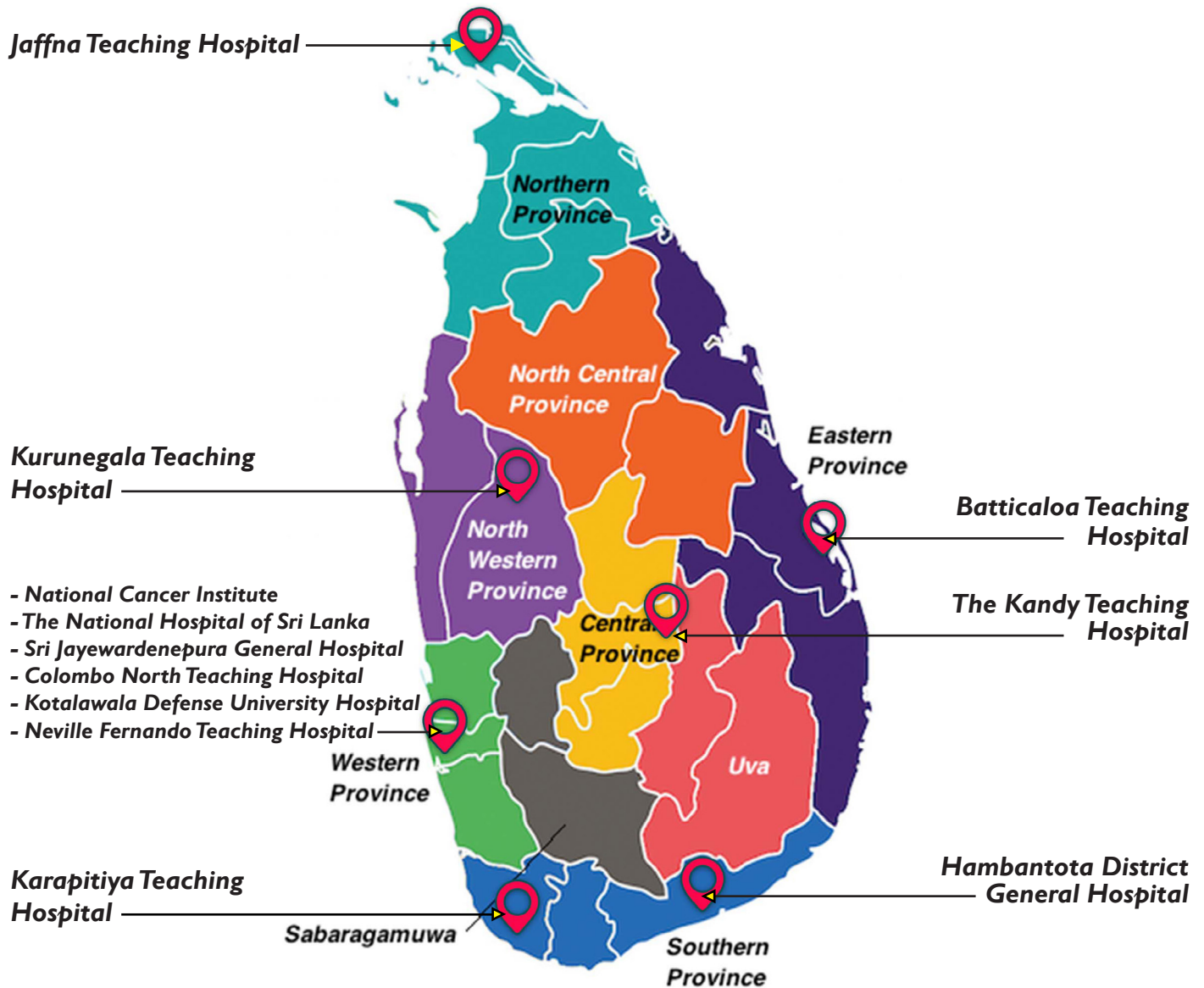
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Major Oncology Treatment Centers

Specialized surgical oncology units have been established in nine provincial hospitals to treat cancer patients in Sri Lanka.



Services at Tertiary Care Oncology Centres

- Surgical oncology
- Chemotherapy
- Radiotherapy
- Individual compassionate counselling
- High end radio-diagnosis PET services and pathology services
- A dedicated in-patient facility
- Out-patient consultation service
- Transfusion programmes
- Day Unit (HDU) facility for day chemotherapy/ out-patient chemotherapy/ patient monitoring and other procedures

Tertiary care cancer centers are equipped with linear accelerators.



Past Clinical Trials

- Breast Cancer

02 Sites				
12 Subjects screened		10 subjects randomized		
Multicounty	Global CRO	Phase III Program		
Submission to first patient in within 18 weeks	No major or critical audit findings	Critical trial experienced investigators	100% recruitment	100% Retention

02 Board Certified Oncologists
15 other medical staff
2 coordinators
Temperature controlled IMP management – Intravenous
Long term archival for 10 years and destruction of unusual IMP
FDA submission trial

- Head & Neck Cancer

03 Sites				
70 screened		58 Enrolled		
Multi-centre	Global Sponsor & CRO	Phase II Program		
Phase III Program	15% of global enrolment	No major or critical findings	Sponsor and CRO audits	100% Retention & follow-up

04 Consultant oncologists and 04 oral and maxillofacial surgeons
35+ medical staff
Intravenous delivery of IMP
FDA submission
Shorter startup timeline – 16 weeks
Recruitment increased 2 times

- Colorectal Cancer

06 Sites				
42 individuals screened		30 Enrolled		
Multi-centre	Global Sponsor & CRO	Phase III Program		
Phase II study was initiated first & ongoing	Followed by phase III study and open label extension	No major or critical findings so far	Sponsor and CRO audits	100% retention and follow-up

03 Board certified consultant oncologist
20 medical staff
Oral IP administration
FDA submission
Shorter startup timeline – 14 weeks
Recruitment increased 1 time

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Neuroendocrine Tumors

Disease prevalence in Sri Lanka:

According to the latest statistics published by the National Cancer Control Programme (NCCP) 2010 -2019, the figures are as follows;

Neuroendocrine tumors		
Originated in	Total number of cases	Male : Female
Stomach	2	1:1
Colon	27	2.9:
Lung	17	4.7
Oesophagus	4	-
Ovary	4	-



Neuroendocrine tumors (NETs) are a heterogenous group of tumors arising from a variety of neuroendocrine cell types.



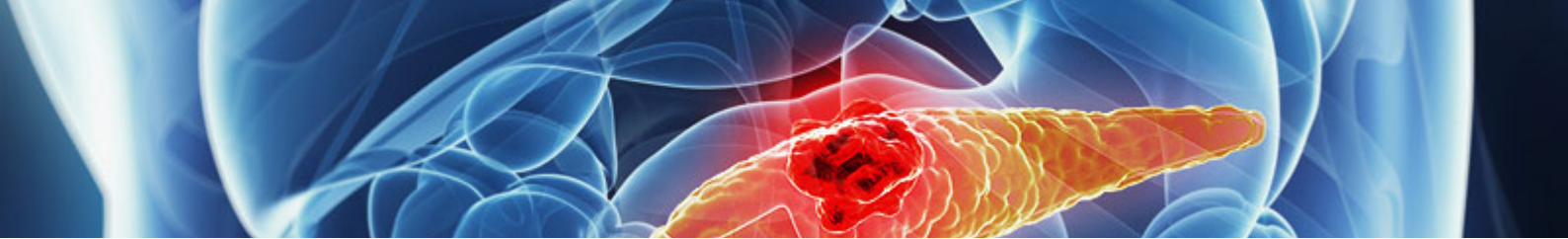
These tumors are relatively rare, though increasing rapidly in prevalence; incidence and prevalence of NET have markedly increased over the last three decades.

54
In 10 Years

Total reported NETs over a period of ten years from 2010 to 2019 according to NCCP data was 54.

However, the statistics regarding neuroendocrine tumors of the hepato biliary region and small bowels were not included in that national survey by NCCP during that period. Therefore, the actual incidence of NETs in Sri Lanka would be higher than the reported figures. According to the literature NET, the second most common GI cancer after colon cancer, is known as the most common in the small intestine (30.8%), pancreas (12.1%), stomach (8.9%), and appendix (5.7%) The latter generally exhibit a more aggressive phenotype in comparison with tumors from other sites and, depending on the cell type of origin (α , β , etc.),

Symptoms are often minimal or absent in initial stages and often misdiagnosed due to vague symptoms. Hence delayed diagnosis is a common occurrence. In addition, the symptoms of NETs are often nonspecific hence could be easily misinterpreted. The clinical presentation and biological characteristics such as local invasion, fibrosis, and metastatic potential of gut tumors vary considerably depending on the anatomical site, neuroendocrine cell(s) of origin (ECL, EC, D, G), and secretory products.



The measurement of chromogranin A (CgA), is a water-soluble acidic glycoprotein stored in the secretory granules of neuroendocrine cells, and its detection in plasma can be used as a general tumor marker for GEP-NENs including 'nonfunctioning' tumors.

- Plasma CgA levels are sensitive (70–85%) markers of GEP-NENs.
- Urinary 5-hydroxyindole-5-acetic acid (5-HIAA; 24 h measurement), the degradation product of 5-HT, is a useful laboratory marker which is generally indicative of the hormonal secretory capacity of the NET.

Specific gastrointestinal hormones which could be secreted either alone or in combination could be biochemically assayed, aiding in the measures taken to control the symptomatology.

In Sri Lanka the basic diagnostic biochemical assays such as CgA and 5 HIAA are available; however, the specific serum/ tissue immunohistochemistry markers are not available. Specific radionuclide imaging modalities used for the localizing of NETs such as OctreoScan, DOTATATE/ DOTANOC etc are a fundamental requirement for the evaluation and management of these tumors, however the unavailability of such imaging facilities has created a great deal of difficulty in caring for these patients. Only the individuals who could afford these scan from neighboring countries get the opportunity of getting the condition accurately localized.

The rate of proliferation of NENs can be quantified by counting the number of mitoses per high powered field on a hematoxylin- and eosin-stained slide, or by counting the percentage of cells that stain positive with the Ki-67 antibody. The defining quality of **Ki-67 as a 'proliferative'** marker is an exclusive expression by dividing cells in the S, G2, and M phases of the cell cycle. The Ki-67% has been widely accepted as the cardinal feature of tumor grading.

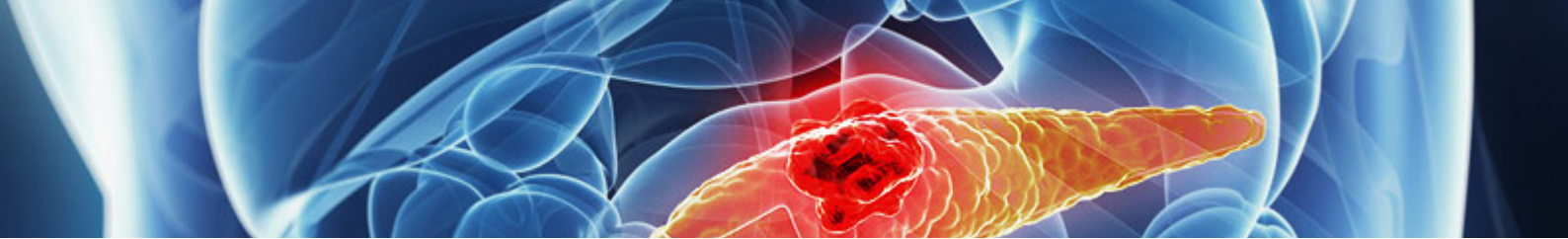
G1

NENs, the prognostic value of the Ki-67% separates NENs into NET grade I (NET G1)

G2

NET grade 2 (NET G2) neuroendocrine carcinoma (NEC) by Ki-67% of ≤ 2 , 3–20, and > 20 % respectively.

Chomogranin A is the most commonly used biomarker but has limitations as does the proliferative marker Ki-67%, which is often used for tumor grading and determination of therapy.



The choice of treatment for NET is surgery.

Therapeutic decisions for inoperable GEP-NENs is a challenge due to the variety of NET types,

- The absence of comparative data for many of the therapeutic approaches
- The numerous disciplines involved in the development of a personalized management strategy.

Recently the data have become available from placebo-controlled studies, which support the value of specific drugs with its use in individual tumor types based on the identification of specific molecular targets. Until recently, the only approved drugs for the treatment of NENs were the SSAs (octreotide LAR and lanreotide). These two classes of agents act as secretory inhibitors by targeting tumor cell receptors and may also inhibit tumor cell proliferation.

Being a developing country, it was a privilege that all NET patients received these drugs free of charge by the Ministry of Health Sri Lanka up until the current economic crisis. Unfortunately, at present these two drugs are not freely available as the cost of treatment is unbearable to the National Health Budget.

We propose that Sri Lanka could be introduced as a suitable destination to facilitate novel treatment options for the neuroendocrine tumors through research and clinical trials. We have the required patient base, highly qualified medical professionals and a well-developed healthcare system.



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Rare Nephrological Disorders in Sri Lanka

Disease Burden

- Kidney Disease Deaths in Sri Lanka reached 6,858 or 5.91% of total deaths.
- Chronic Kidney Disease is the major kidney disease prevalent in Sri Lanka (5th major cause of death in 2019. [2])
- The incidence of Chronic Kidney Disease in Sri Lanka has been doubling every four to five years, so that currently >150,000 people are affected by the disease and about 3% of them lose their lives annually.
- As per literature and past work many rare nephrology diseases are more prevalent in Sri Lanka. Such as, [4]
 - Complement 3 Glomerulopathy (C3G)
 - Focal Segmental Glomerulosclerosis (FSGS)
 - Immunoglobulin A (IgA) Nephropathy
 - Lupus Nephritis (LN)
 - Systemic lupus erythematosus (SLE)

Common Nephrological Diseases in Sri Lanka

Disease	Epidemiology data	Local Standard of Care
Chronic Kidney Disease of Unknown etiology (CKDu)	The prevalence of CKDu is the predominant form of CKD in Sri Lanka and the prevalence ranges from 8 % – 21% [1]	Control of hypertension and prevention of further exposure to toxins
IgA nephropathy	2-5 per 100,000 population [2]	ACE-Is / ARBs / Prednisone / Immunosuppressive agents
Lupus Nephritis	50 – 60 per 100,000 population [2]	Methylprednisolone + cyclophosphamide / mycophenolate mofetil / AZA
SLE	5 – 70 per 100,000 population [2]	Immunosuppressive drugs / Prednisone
Complement 3 glomerulopathy (C3G)	Approximately 1 – 1.5 % [2]	Control of hypertension (ACE-Is / ARBs) / Statins / Cyclophosphamide Mycophenolate mofetil (MMF) / Tacrolimus



Epidemiology of CKD in Sri Lanka – source WHO 2020

Etiology provinces n (%)	Western province (%)	Other
Diabetic nephropathy*	26 (37.7)	11 (21.6)
Hypertension	8 (11.6)	8 (15.7)
Glomerulonephritis	6 (8.7)	6 (11.7)
Unknown	17 (24.6)	14 (27.4)
Obstructive uropathy	4 (5.8)	6 (11.8)
Adult polycystic kidney disease	4 (4.8)	3 (5.9)
Interstitial disease	1 (1.4)	2 (3.9)
Others	3 (4.3)	1 (1.96)
Total	69 (100)	51 (100)

Services at Tertiary Care Nephrology Centres

- 24 hour on call for renal service	- Counselling and pre transplant workup clinics
- 24 hour acute haemodialysis (HD) services for emergencies	- Post-transplant clinics
- Rehabilitation programs	- Hemodialysis clinics
- Renal biopsy services	- Mobile dialysis service

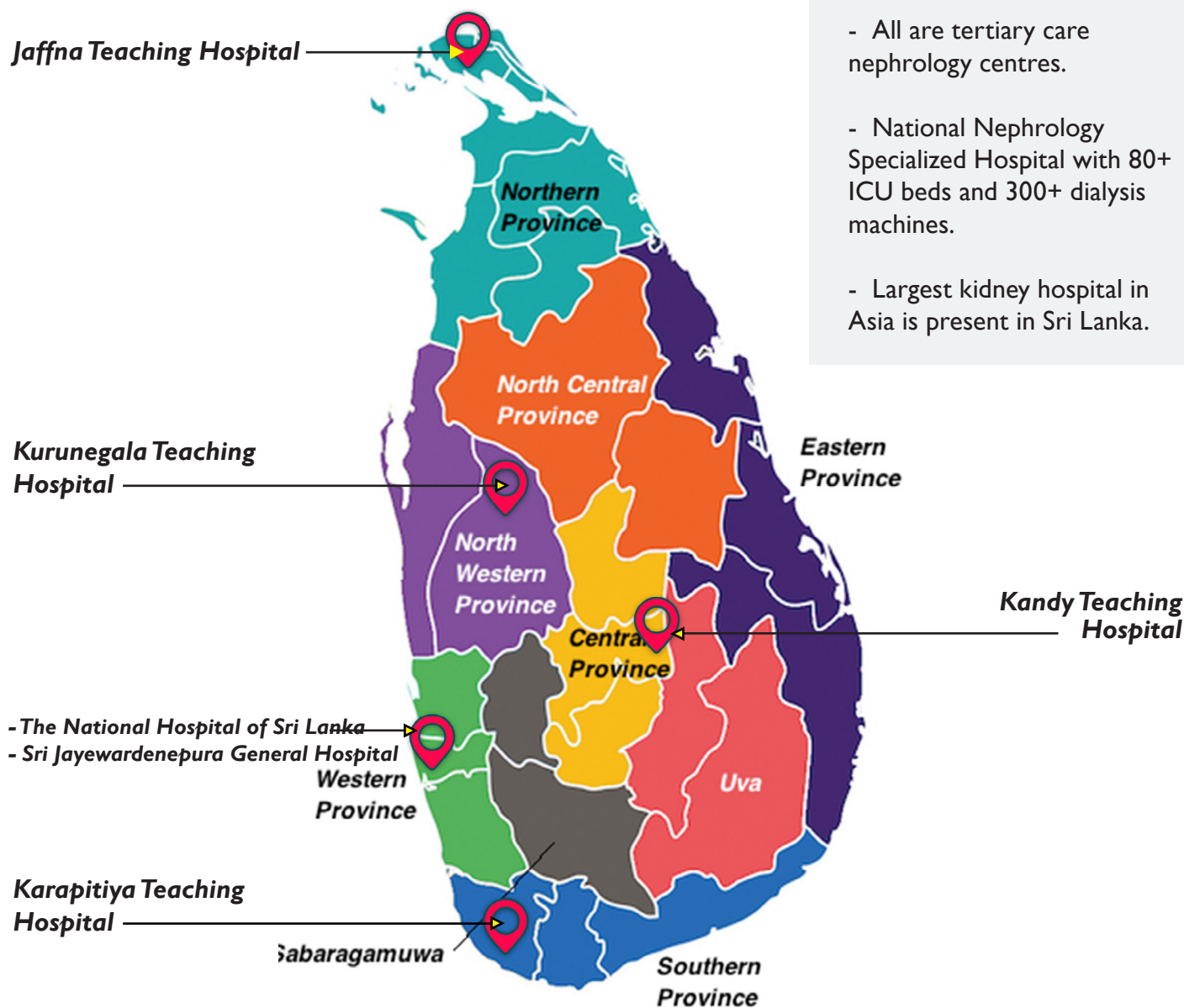
Tertiary care cancer centers are equipped with linear accelerators.

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Major Nephrology Treatment Centres



- All are tertiary care nephrology centres.
- National Nephrology Specialized Hospital with 80+ ICU beds and 300+ dialysis machines.
- Largest kidney hospital in Asia is present in Sri Lanka.

Clinical Trial Experiences -Remediumone

Sri Lanka has the capacity of executing projects as per the international standards because we at RemediumOne provide complete management services from submission to close out.

For the past 13 years, RemediumOne is managing multiple, pivotal, and complex clinical trials in Sri Lanka for Industry partners and global centers of excellence with excellent quality, without any critical or major audit findings.

References:

[4] Wijewickrama, Eranga S., et al. "Epidemiology of chronic kidney disease in a Sri Lankan population: experience of a tertiary care center." Saudi Journal of Kidney Diseases and Transplantation 22.6 (2011): 1289. <https://www.sjkdt.org/text.asp?2011/22/6/1289/87258>



Past (completed) Clinical Trial Experience in Nephrology

- Systemic Lupus Erythematosus

04 Sites				
42 Subjects screened		24 subjects randomized		
Multicountry	Global CRO	Phase II Program		
Submission to first patient in within 18 weeks	No major or critical audit findings	Critical trial experienced investigators	100% recruitment	100% Retention

02 Board Certified Nephrologist
18 other medical staff
1 coordinator per site
Temperature controlled IMP management – Intravenous
Long term archival for 10 years and destruction of unusual IMP
FDA submission trial

- Lupus Nephritis

05 Sites				
53 screened		34 Enrolled		
Multicountry	Global Sponsor & CRO	Phase II Program		
Phase III Program	12% of global enrolment	No major or critical findings so far	Sponsor and CRO audits	100% Retention & follow-up

05 Consultant Nephrologist
30+ medical staff
Subcutaneous delivery of IMP
FDA submission
Shorter startup timeline – 16 weeks
Recruitment increased 2 times

- Immunoglobulin A Nephropathy

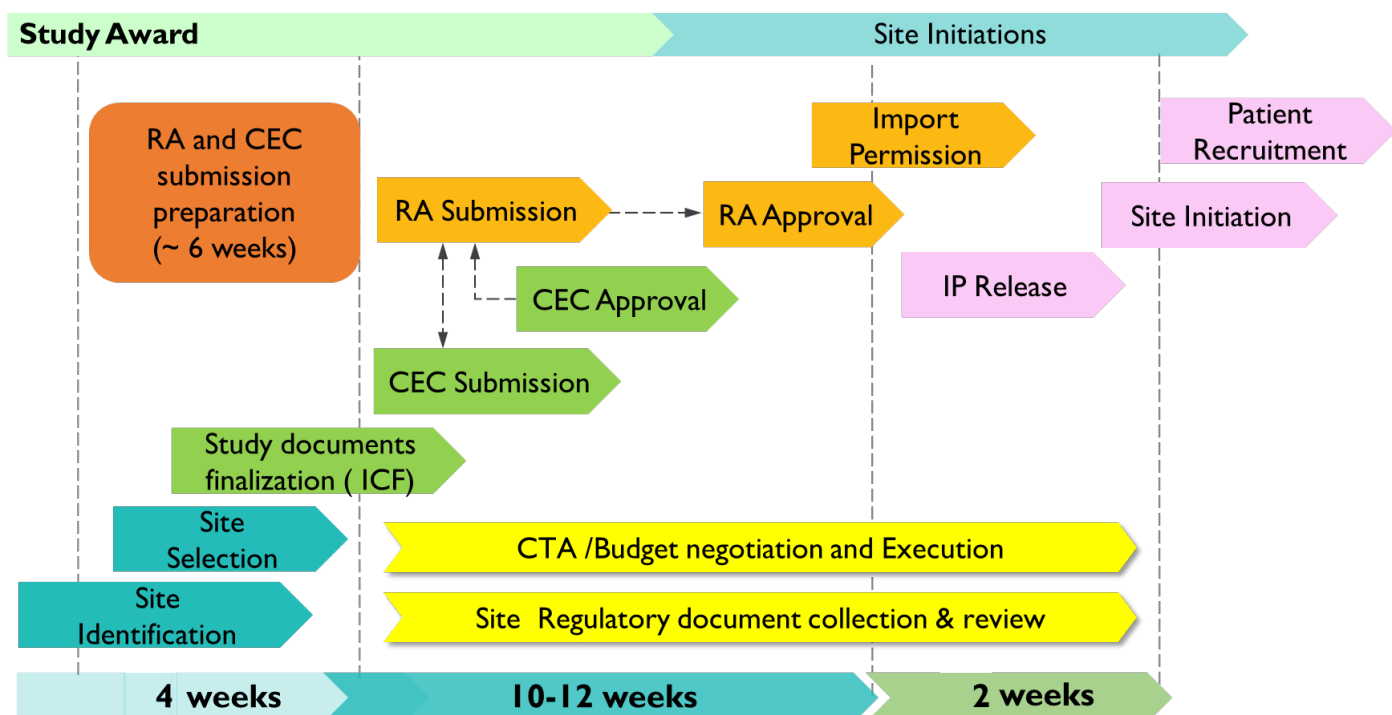
05 Sites				
09 Individuals screened		05 Enrolled		
Multicountry	Global Sponsor & CRO	Phase II Program		
Phase II study was initiated first and ongoing	Followed by phase III study and open label extension	No major or critical findings so far	Sponsor and CRO audits	100% Retention & follow-up

05 Consultant Nephrologist
22 medical staff
Intravenous IMP/ inpatient admissions
FDA submission
Shorter startup timeline – 14 weeks
Recruitment increased 1 times

Through mutually beneficial partnership RemediumOne will be able to support you to conduct clinical trials in Sri Lanka. We would be able to support you through our network of 300+ Principal Investigators from different therapeutic areas.



- Average startup timeline: Submission to FPI 16-18 weeks



What we can offer:



05-06 Investigator sites with prior experience



Submission to First Participant In (FPI) in 16-18 weeks



No major or critical audit findings



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