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United Kingdom primary Sjögren's syndrome registry (UKPSSR) – A united effort to tackle an orphan rheumatic disease

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Abstract

Primary Sjögren's syndrome (pSS) is a multi-system autoimmune disease with a prevalence and health economic impact that are comparable to rheumatoid arthritis. However, pSS research has been relatively poorly supported. The creation of a large cohort of clinically well-characterized pSS patients will provide a catalyst and valuable resources to promote high quality pSS research. In this review, we will describe the creation of such a cohort and the associated research biobank that is currently being established in the United Kingdom (UK) entitled United Kingdom primary Sjögren's syndrome registry (UKPSSR). We will discuss the strengths and weaknesses of the design of the registry and highlight the key challenges in the establishment of the registry and the strategies that we employ to overcome these barriers. Finally, we will consider the future development of the UKPSSR including utilisation and maintenance of the cohort.

Primary Sjögren's syndrome is a significant healthcare burden

Primary Sjögren's syndrome (pSS) is a chronic multi-system disease affecting approximately 0.3-0.5% of the adult population in the western world, making it the second most common autoimmune rheumatic disease [1,2]. The true prevalence of pSS may be considerably higher because many patients may remain undiagnosed as their presenting complaints are often non-specific. Women are 9 times more likely to be affected than men [1-4]. The disease is characterised by oral and ocular dryness, fatigue and musculoskeletal pain. In addition, pSS can affect other organs including the kidneys, lungs, skin and the nervous system [3,4]. More importantly, patients with pSS have a greater than 40-fold increased risk of developing lymphoma [4, 5]. Patients with pSS have poor health-related quality of life and a significant proportion of pSS patients are unable to work due to their condition [2, 6-17]. In a recent study, a conservative estimate of the total annual indirect costs for patients with pSS was £7,677, comparable to that for patients with RA (£10,444) but significantly higher than that for healthy controls (£892) [18]. Therefore, pSS is not a benign condition, as often perceived by clinicians and non-clinicians alike, but a significant health and economic burden to the patients and society.

There is a large unmet need in pSS research and management of pSS patients

The pathogenesis of pSS is unclear but is generally considered to be a consequence of autoimmunity. This conclusion is largely based on the observation of inflammatory infiltrates in the affected exocrine glands and the presence of characteristic autoantibodies against RNA-binding proteins Ro and La. What triggers the inflammatory response, however, is poorly understood. Furthermore, the pathophysiological basis for

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the systemic manifestations of pSS such as fatigue and other organ involvement has not been defined. It is therefore unsurprising that no effective treatment is currently available for pSS.

A literature search in February 2010 using Pubmed Central, the US National Institutes of Health digital archive of biomedical and life sciences journal literatures, retrieved 10,413 articles when using the keywords "Sjogren's syndrome" (and only 3066 if "primary Sjogren's syndrome" was used), compared to 100,928 articles when the keywords "Rheumatoid arthritis" was used. The contrast was even more striking when the searches were limited to "humans" and "clinical trial", with only 260 articles for "Sjogren's syndrome" compared to 5940 for "rheumatoid arthritis". While these measures are crude, it highlights the paucity of research in pSS considering the prevalence and health economic impact of a condition that has no effective treatment.

The reasons for the lack of progress in pSS research are not clear but several possible explanations exist. Firstly, previous studies have often used different diagnostic criteria and outcome measures making comparison of data from different studies difficult. In addition, the sample sizes of many studies were often too small for meaningful conclusions to be drawn. Furthermore, detailed corresponding clinical data were often unavailable. Secondly, many clinical measurements of exocrine glandular function such as Schirmer's test and unstimulated salivary flow do not have sufficient sensitivity to reliably distinguish pathophysiological processes of inflammatory activity, acinar gland damage or acinar cell loss. Furthermore, many patients with pSS often present late, hence researchers using samples from these patients may inadvertently limit their investigations

and thus bias their findings to the late-stages of the disease. Finally, pSS research has not received the level of public or commercial funding support of conditions such as RA.

Taken together, these observations indicate that there is a large unmet need in pSS research and that additional infra-structure is necessary to support and stimulate high quality clinical and academic research into this disease. In this regard, the creation of a cohort of clinically well-characterised patients with pSS and the creation of a research biobank could provide a much needed resource and catalyst for pSS research.

Recent advances in pSS research have created an optimal environment for the development of a national registry for pSS

Despite the obstacles in pSS research set out above, some key progress has been made in pSS research over the last decade which has laid the foundation for a national cohort of pSS mentioned above. Firstly, through the effort of researchers in Europe and across the world, a consensus was reached on the classification criteria [19] for pSS and a core set of outcome assessment tools developed [20-26]. As a result, standardised approaches to data collection and analysis are now possible. Furthermore, these projects have galvanized the formation of the UK Sjögren's Interest Group (UKSIG), a network of clinicians and scientists with an interest in pSS, as well as prompting the creation of many clinical databases of pSS patients among members from their own practices. Secondly, advances in clinical and laboratory investigative technologies including the emergence of high-throughput technologies such as proteomics and genomics which allow systematic analysis of genome composition and gene expression profiling has

opened up new avenues in dissecting the molecular basis of pSS and thus the potential for future, targeted drug development.

The UK primary Sjögren's syndrome registry

The UK primary Sjögren's syndrome registry (UKPSSR) is intended to be a cohort of 500 clinically well-characterised patients with pSS fulfilling the AECG consensus criteria. The UKPSSR is funded by the Medical Research Council, UK. The primary objective of the UKPSSR is to promote high quality clinical research and facilitate clinical trials of pSS. In addition, it is hope that the establishment of the UKPSSR will foster collaborative research and enhance the profile of pSS research within a wider community.

All patients recruited will be assessed for disease activity and damage, together with other detailed, relevant clinical information including data on quality of life using appropriate validated instruments. In addition, all cases will be assessed for their fulfilment of the AECG consensus criteria for pSS and cases that do not fulfil the criteria will be excluded. Table 1 summarises the clinical data that are being collected for the registry. All data, including subjective and objective clinical assessments and patient reported outcomes, are being collected using a standardised proforma. To facilitate clinical data collection, a web-based database has been developed so that recruiting clinicians have the option to enter the clinical data at source. This resource may reduce the risk of data loss during transfer and improve the efficiency of clinical data collection. In addition to clinical data collection, peripheral blood samples are taken from the participants for the extraction of serum, DNA and RNA which are stored for future

research. Therefore, the UKPSSR is more than a patient cohort, but also an epidemiological research project as well as a research biobank.

Recruitment started in August 2009 and is due to complete in March 2012. There are currently 28 centres across the UK among the UKPSSR study group. However, new recruitment sites will be considered until the recruitment target is reached. The advantages of not limiting recruitment to a few large centres are two fold. First, it will increase the likelihood of achieving the recruitment target. Second, it will create a cohort that better represents the full spectrum of patients with pSS across the UK. However, quality assurance of a large number of recruiting sites can be problematic, and we will discuss how we address this issue later.

Since the ultimate goal of the UKPSSR is to facilitate high-quality pSS research, it is important that all the resources of the UKPSSR (including the anonymised clinical data and biological materials) are widely accessible by researchers while at the same time to put in place a robust mechanism to ensure that the resources will only be used for high quality research, in particularly for the resources that are finite (e.g. serum and RNA). The strategies that we employed to achieve this goal are summarised in Table 2.

Potential weaknesses of the UKPSSR

While we believed that the UKPSSR is a highly meritorious project, we recognise that there are several potential weaknesses in its design. Firstly, we do not collect salivary gland biopsy samples, saliva or tears. Since the primary organs affected in pSS are the salivary and tear glands, studying the biopsy or other biological materials taken from these affected sites could be more informative in understanding the pathogenesis of pSS.

The collection of salivary gland biopsies was considered at the planning stage of the UKPSSR, however, the idea was abandoned because all the patients taking part in this study already have a definite diagnosis of pSS and salivary gland biopsy is therefore not clinically indicated. Furthermore, many of the recruiting centres do not have easy access to a salivary gland biopsy service. Regarding saliva, there was a debate on whether whole saliva or saliva directly collected from the major salivary glands was more appropriate and concerns were raised regarding the utility of saliva in pSS research. As for tear samples, we anticipated that collection of tears could be difficult or impossible for many patients, although impression cytology of the conjunctival cells may be an alternative. The need for collecting salivary gland biopsy, saliva and tear samples will be re-evaluated during the interim data analysis when 250 patients are recruited. Secondly, as salivary gland biopsy is often not performed in the diagnostic algorithm for Sjögren's syndrome in the UK, and because the AECG consensus criteria require the presence of either anti-Ro or -La antibodies or a positive salivary gland biopsy [19], we anticipate an over-representation of pSS patients with anti-Ro or –La antibodies in our cohort. Since the clinical features of anti-Ro/La$^+$ pSS patients differ from those without the autoantibodies, the potential bias of anti-Ro/La$^+$ pSS patients in the registry should be taken into account when the data are analyzed. Additionally, we will consider the creation of a smaller comparative cohort of anti-Ro/La$^-$ pSS patients in the future. Thirdly, the majority of the collaborating recruitment centres are secondary care rheumatology units, and since pSS patients without other systemic clinical manifestations may be managed by specialists in dentistry, oral medicine, ophthalmology or the general practitioners and not by rheumatologists, the UKPSSR could bias against patients with

predominantly dryness symptoms. Fourthly, since a large number of centres participate in the recruitment for this project and since the clinic settings of individual recruitment centres varies, recruiting clinicians can decide on the most efficient case finding strategy for their recruiting sites for pragmatic reason. However, we do recommend recruiting clinicians, if possible, to use their existing databases or clinic records in order to identify pSS patients under their care and send invitations to all such pSS patients to take part in this project to reduce the risk of under-ascertainment. Furthermore, all recruiting clinicians are required to maintain a screening log. Thus, our cases can either be identified through existing databases, or during routine clinical appointments or both. Recruiting clinicians who run a dedicated pSS clinic and those who use an active case ascertainment approach to identify cases are more likely to achieve complete case ascertainment. On the other hand, an *ad hoc* approach to identify cases is likely to result in under-ascertainment and may also affect the quality of the data obtained. In addition, this project requires patient consent which may lead to self-selection bias of pSS patients who are more motivated. Therefore, the UKPSSR is a convenience sample and subject to the potential sampling bias associated with this approach including non-representation of the population and did not identify the entire pSS population. However, the involvement of a large number of recruitment sites across the UK and the relatively large sampling size should reduce the risk of such bias associated with convenience sampling. Nevertheless, it is important that investigation of the factors that can affect case ascertainment should be carried out upon completion of recruitment and attempt should be made to correct such sampling bias when the data are analyzed. Fifthly, this is not an inception cohort and we anticipate that many patients of the UKPSSR cohort will have a

relatively long duration of the disease. However, as many patients with pSS often have many years of symptoms of dryness and other clinical manifestations such as fatigue and musculoskeletal pain before they seek medical advice, especially in a secondary care setting, it is a considerable challenge to accurately determine when the disease begins. Therefore, limiting the recruitment to "newly diagnosed" patients may not significantly improve the recruitment of patients with early disease, but instead will have a significant negative impact on recruitment rate. One approach that may facilitate the recruitment of patients with early stage of the disease is to screen all patients with sicca symptoms for pSS. In this regard, a recent study carried out in an early arthritis clinic in which anti-Ro and –La antibodies were routinely tested showed that while over 46% of patients reported sicca symptoms, none of the patients were positive for either the anti-Ro or anti–La antibodies. With the exception of one patient, none has undergone salivary gland biopsy (Hegarty et al, personal communication). Nevertheless, this observation suggests that the yield of diagnosing pSS according to AECG consensus criteria using this screening approach may be low, at least in an early arthritis clinic setting. It would be interesting to investigate whether such an approach may be more productive in oral medicine or ophthalmology clinics. It is also noteworthy that the Sjögren's International Clinical Collaborative Clinical Alliance (SICCA) is setting up a research biobank and registry of patients and family members with sicca symptoms or other autoimmune features without the requirement of fulfilling the classification criteria of the AECG [27], it will be interesting to compare the data generated by the UKPSSR and that of the SICCA registry. Finally, the UKPSSR is a cohort of patients from the UK only, therefore, it remains possible that it is not representative of patients with pSS in other parts of the world,

although thus far, there is no strong evidence to suggest that there are significant geographical variations in the clinical features of pSS, at least within European populations.

Challenges

The key challenge for the UKPSSR is achieving the recruitment target. As of mid May 2010, a total of 175 pSS patients have been recruited, 9 months after recruitment has started. Although the data appear to be encouraging, a closer examination of the data revealed that there are only 10 centres actively recruiting, 5 centres in the preparation stage for recruitment, but almost half of the recruiting centres have not yet obtained the necessary regulatory requirement for taking part in recruitment, including several centres that are anticipated to recruit a high number of patients. The lengthy delay in obtaining the relevant regulatory approvals for this project was unexpected. Although under the Research Governance Framework in the UK, there is no requirement for local approval from the Research and Development (R&D) department of the recruitment centres, however, in practice, because of the potential impact on clinical services of the recruitment centres, approvals from the local R&D department is essential for most recruitment sites. In the UK, the infra-structure support for clinical research is provided by the UK National Institute of Health Research (NIHR). The recent changes to the NIHR funding strategies for clinical research means that funding for and access to the clinical research support infra-structure such as research nurses, clinic time and space, will be limited to studies that have been adopted as approved "portfolio" studies by the NIHR comprehensive local research networks (CLRN). The aim of the "adoption

process" is to ensure that the funding will be used to support only high quality clinical research projects. However, this has created a significant barrier for the UKPSSR recruitment because although the registry is clearly created with the aim of facilitating clinical and academic research, and will generate invaluable epidemiological data, it lacks a "clearly defined" research question to be addressed. Such a question is an essential requirement for the study to be approved by the UK NIHR CLRN and consequently the UKPSSR has not been adopted into the portfolio of the NIHR approved studies to date. This fact has had important repercussions for our recruitment sites as many are heavily reliant on the support of the clinical research infra-structure in order to take part in recruitment. To circumvent this obstacle, the UKPSSR has made a further application for NIHR CLRN approval using a substudy of the registry which is designed to assess the cardiovascular risk of pSS patients. This substudy has now been approved as a NIHR portfolio study. Since the substudy is a study that utilises the majority of the clinical data/samples collected for the UKPSSR main study with additional study-specific assessment, in practical terms, the UKPSSR project has now been approved by the NIHR CLRN. We anticipate that this approval will have a significant beneficial impact on the progress on gaining local R&D approvals as well as attracting new recruitment sites.

Another major challenge is to quality assure the UKPSSR data and samples especially when a large number of centres are involved in the recruitment. Several measures are used to ensure the robustness of our data and quality of our samples. Firstly, during the set-up phrase of the registry, we held a series of meeting inviting all the recruiting clinicians and patient representatives to discuss all aspects concerning the recruitment process such as the design of the proforma and database, patient identification and

selection, the organisation of recruitment, data and sample collection and strategies to secure research infra-structure support. This consultation process helped to develop a protocol that is as feasible and practical as possible without compromising the design of the registry. Secondly, adequate training and support for recruiting staff is provided. This is accomplished through group training meetings, one-to-one training during initiation site-visits and opportunity for recruiting staff to "shadow" the recruitment process. In addition, a dedicated senior research nurse for the registry will provide support and answer queries regarding the recruitment procedure. Thirdly, formal written agreements and protocol are set up. Regarding the samples, supply agreements are in place between the UKPSSR and the recruitment centres defining the standards expected of the procurement procedures and the transfer of the samples as well as the responsibility of the recruiting sites and the receiving organisation. In addition, standard operation procedures are in place to cover all aspects of the recruitment procedures. Nevertheless, in this project, comprehensive clinical information is being collected which can be particularly challenging if patients are recruited during routine outpatient appointments. Therefore, the recruiting clinicians need to be highly motivated, vigilant and dedicated. Furthermore, the quality of the clinical data will also depend on the quality of the medical records available at source. Therefore, another key measure for quality assurance is monitoring and audit. In this regard, all the data will be checked for accuracy and completeness. Any mishandling of the samples is recorded and an audit trail will be kept. Formal audit will be carried out at least once during the lifetime of the project.

Another important challenge for the UKPSSR is to maximise the utilisation of the cohort and the resource of the UKPSSR for high quality pSS research. To date, the cohort is

being used for a mixture of ongoing clinical and academic projects including the assessment of cardiovascular risk in pSS, the investigation of the link between anti-muscarinic receptor and pSS, genetic association studies organised by the Sjögren's Genetics Network as well as the validation of pSS assessment tools organised by the European League Against Rheumatism (EULAR) Sjögren's syndrome study group. In addition, the cohort will also be utilised for patient selection for a planned multi-centre randomised placebo-controlled clinical trial of rituximab in patients with pSS. We have outlined earlier the strategies that we use to maximise the utilisation of the cohort in Box 2, but it remains to be seen how effective these strategies will be. In particularly, one of the strategies is to create a parallel cohort of age-, sex- and gender-matched healthy controls. Thus far, the rate of healthy controls is relatively slow with just under 20 participants after a six-month recruitment period. This is partly because our current emphasis on achieving the recruitment target for pSS patients, but may also be a result of the recruitment method used. Currently we use the "find a friend" approach, in an attempt to create a cohort that is not only age-, sex- and gender-matched, but also matches for geographical and social parameters. Nevertheless, contingency plan is in place for healthy controls recruitment through open advertisement in key recruitment centres if our recruitment target is not reached.

Finally, a longer term challenge for the UKPSSR is the maintenance and development of the cohort as well as the long-term storage of the samples which will require securing of further funding to support the necessary personnel and consumables cost.

Future development

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Our vision is that the UKPSSR will be the foundation of a long-term collaborative project. Therefore, it is important that we look ahead to the future development of the registry. Firstly, we plan to collect longitudinal data at 3-5 years after the inception, and every 5 years subsequently. In this regard, the UKPSSR is modelled on a successful rheumatology cohort, the Norfolk Arthritis Register [28]. Longitudinal study of the cohort will not only generate valuable data on the natural history of pSS, which is at present poorly understood, but also important in the evaluation of systemic features such as pulmonary manifestations, peripheral neuropathy and lymphomas which are more common in patients with longer disease duration [29, 30]. In addition, the creation of a disease-control cohort will facilitate the utilisation of the UKPSSR data and samples. Suitable disease controls may include patients with secondary Sjögren's syndrome or other connective diseases such as lupus and rheumatoid arthritis (with or without secondary SS). Furthermore, it may be desirable to develop additional smaller pSS cohorts with particular clinical features such as an "inception cohort", "anti-Ro/La⁻ cohort" and a "systematic population sampling cohort" in order to address some of the potential weaknesses relating to the sampling methods used in the creation of UKPSSR.

As mentioned earlier, we have developed a web-based database for clinical data collection for the UKPSSR. We envisage that the data from the registry will guide us to develop a simplified downloadable version for clinicians to use for their day-to-day management of pSS patients. This database will not only improve the standard of care of pSS patients but also facilitate standardisation of data collection which in turn will facilitate future research and clinical audits.

Thirdly, we hope to form a collaborative network with other pSS registries across the world and to reach a consensus on a core data set that is important for all pSS registries. Such a consensus can promote data sharing, increase the power of the data analysis and ultimately benefits pSS research and patient care.

Conclusions

To conclude, the UKPSSR will enhance pSS research through facilitating clinical and academic studies as well as generating an invaluable set of epidemiological data. The registry could bias against pSS patients negative for anti-Ro and La antibodies, and the lack of salivary gland samples could reduce the utility of the biobank. The key challenge for the UKPSSR is achieving the recruitment target and ensuring the standards of the data and samples collected are high. The difficulty was compounded by the delay in obtaining the relevant regulatory approvals and the potential loss of clinical research infra-structure support in some recruitment centres. Therefore, it is clear that the creation of the UKPSSR required the enthusiasm, commitment and hard work of all the UKPSSR study group members. The ultimate success of the UKPSSR, however, will be measured by its utilisation for high quality pSS research and the future development of the cohort. In the longer term, it is hoped that the UKPSSR will serve as a foundation for the formation of a more extensive collaborative research network for pSS.

Key Messages

1. UKPSSR is a national cohort and research biobank of 500 clinically well-characterised pSS patients.

2. Key challenges are archiving the recruitment target and quality assurance of the data and samples.

3. The success of the UKPSSR will be assessed by its utilisation for pSS research.

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Clinician's Assessment	Patient Reported Outcome
1. AECG consensus criteria	1. Symptom assessment
	- PROFAD-SSI
2. Demographics	- ESSPRI
	- Epworth Sleepiness Scale
3. Treatment (pharmacological and non-pharmacological)	- Orthostatic symptoms scale
	2. Quality of life
4. Co-morbidity	- EQ-5D
	- SF-36
5. Disease activity*	
- ESSDAI	3. Anxiety and depressive symptoms
- SCAI	- HAD
- SSDAI	
	Optional
6. Disease damage	4. Autonomic symptoms and cardiovascular risk
- SDI	- COMPASS
- SSDDI	- Lifestyle (smoking, physical activity)
Optional	
7. Cardiovascular risk assessment	

Table 1. The categories of clinical data that are collected for the UKPSSR and the outcome measure tools used for the data collection. Abbreviations: ESSDAI, SCAI, SSDAI, SDI, SSDDI, PROFAD-SDI, ESSPRI – see main text. EQ-5D: European Quality of life–5 dimensions, SF-36: Short form 36, HAD: Hospital anxiety and depression scale, COMPASS: Composite autonomic symptom scale.

	Strategies
1.Removing Barriers	1. Obtain "generic" research ethics approval for the use of the UKPSSR resources for research directly relevant to pSS
2. Improving Accessibility	1. Open access to all academic institutions and industrial partners both within the UK and abroad. 2. Set up a website for the registry (www.sjogrensregistry.org) 3. Active engagement with researchers who have the expertise and interest in pSS research 4. Promotion of the UKPSSR at appropriate medical and scientific conferences
3. Quality Assurance of research projects	1. Formal application for the use of the UKPSSR is required 2. Applications reviewed by a 7 person steering committee to assess the scientific merits and relevance to pSS research 3. Samples and data will only be released after evidence of adequate financial support and all necessary regulatory approvals are obtained 4. All samples released will be subject to material transfer agreements which ensure that samples are used for specified project, and that the samples will be handled appropriately and in strict confidence
4. Added values	1. UKPSSR can request the researchers utilising the samples/data to send a copy of the data derived if the steering committee judge that the addition of such data will enhance the utilisation of UKPSSR. 2. Establish an age-, gender- and ethnicity-matched healthy control cohort. (The creation of a suitable disease control cohort and other pSS subset is under consideration).
5. Maintenance of high quality samples	1. SOPs for sample collections, processing and storage 2. Use PAXgene collection tubes to ensure high quality DNA & RNA samples 3. Generate EBV transformed cell lines to maintain a permanent source of DNA

Box 2. The strategies for promoting the utilisation of the UKPSSR resources for high quality pSS research.