British Sjögren's Syndrome Association

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# Taking Part in Clinical Studies - Risks and Benefits

*Taken from the AGM 2014 talk by Professor Simon Bowman, Consultant Rheumatologist at the Queen Elizabeth Hospital in Birmingham.*

Professor Bowman is the immediate past President of the BSSA and current President of the British Society of Rheumatology. He opened his talk by acknowledging that there is currently no perfect treatment for SS. He compared this to the situation in Rheumatoid Arthritis where over the last 20 years there has been a dramatic change in the treatment of RA and we are no longer seeing the end stage damage and disability that we used to because of new drugs and early treatment. Professor Bowman discussed new treatment in general, and the drug development process. He explained the steps that a potential new treatment goes through before it becomes available for general use. All new drug treatments have to go through a 'clinical trial' to ensure it is safe and as good as or better than existing treatments.

There are different types of clinical trial but in most cases the first step is to perform an 'open label' trial where you give the drug to a small number of patients in a controlled fashion and observe outcomes. Next a dose ranging study is often needed in the early stages of the development of a new drug to determine the optimum dose.

When performing a clinical trial it is important to bear in mind that the 'placebo effect' (where an individual improves even though they are on the 'dummy drug') can be as high as 20 -30% so the next step is to do a 'randomised placebo controlled' trial where you compare the active drug against a placebo (dummy drug). A standard way of performing this would be to give half the participants the active drug and half the placebo with both the patient and their doctor 'blinded 'to who has what. The process of allocating patients to treatment or placebo is called 'randomisation'. This needs to be done in such a way that it is truly random e.g. by computer or shuffled sealed envelopes to ensure everyone has an equal chance of being allocated to each arm of the study.

In a double blind study (sometimes also called double masked) neither the doctor nor the patients knows which treatment is allocated to whom. In a crossover study there is a change of treatment half way through. Patients may be switched from placebo to active or vice versa. In some studies everyone is switched to active treatment after a defined period of time. It is important to recruit the 'right' people to make sure we discover whether a drug truly works or not. It is important that the research team think carefully about the 'entry and exclusion criteria'. New drugs are being developed and being targeted at certain aspects of the condition. In general you need to look for patients with the characteristics that you want to treat



(e.g. significant tiredness in a study of a treatment for fatigue) and think abut outcomes. The research team will also need to exclude people who have conditions that might affect their response to the drug.

When designing a study you need to think about the number you need to treat to prove an effect bearing in mind the size of the placebo effect (i.e. that 20-30% improvement is likely in the placebo group).

There is a lot of regulation around clinical trials designed to protect patients from harm and all doctors and other staff running clinical trials have to undergo Good Clinical Practice (GCP) training. Several bodies look at the trial in advance of it being approved. In general this is likely to include an ethics committee (usually a group of clinicians and lay people who look at whether the trial is reasonable and likely to be safe) and the MHRA (Medicines & Healthcare Products Regulatory Agency).

There are different development stages for drugs. In the first instance drugs will go through a preclinical study. This is laboratory based and the drug is tested in test tubes and animals. The drug then goes through a series of trials described as Phase 1 – 4:

**Phase 1** – small numbers of often healthy people to ensure it is safe and to determine dose and potential side effects

**Phase 2** – medium size e.g. 100 people, looking at dosage and

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side effects
**Phase 3** – fully powered e.g. 1000+; to confirm effectiveness and look for side effects
**Phase 4** (post licensing studies) – looking for longer term problems and rarer side effects.

Before a drug can be made available to the public in the UK it needs to be 'licensed' but most new drugs also need to be approved by NICE (National Institute for Clinical Excellence) before the NHS will fund them for a particular condition. This whole process can take many years.

One significant problem with running clinical trials is recruiting sufficient patients.

If you are approached to take part in a clinical trial it is likely that you doctor or nurse will discuss the pros and cons of taking part. You should bear in mind the following when making your decision. There may be no direct personal benefit from taking part but bear in mind that the trial may benefit the wider cohort of patients with Sjögren's and increase knowledge of the condition and its treatments so leading to an indirect benefit over time. Clinical trials often require multiple clinical visits and this may make it difficult for individuals to participate. However you are likely to benefit from closer monitoring and a closer relationship with the doctors and nurses treating your condition. It is possible that the new drug being tested may not work, or might cause side effects. The side effects of a new treatment are more unpredictable than those of an established drug. In general you should be given sufficient information on the possible risks and benefits. The participation information sheet should cover all these issues and consent forms should make it clear that participation is voluntary and that you can drop out at any time without having to give a reason.

Professor Bowman then discussed current and future Sjögren's Syndrome trials. At present there are no routinely available treatments that substantially modify the underlying disease. He discussed the TRACTISS trial. This is a randomised, controlled, clinical trial of anti-B-cell therapy in patients with primary Sjögren's. Participants are given two courses of rituximab or placebo. B cells are involved in producing antibodies and Rituximab reduces the levels of B cells in the circulation. Participants were chosen with Primary Sjögren's (Ro +ve) with fatigue and oral dryness but some residual salivary flow and less than 10 years disease duration or some systemic features. This study is still going on and results should be available later in 2015.

TEARS is a similar study that occurred in France but patients were only given one course of rituximab which may have been insufficient and reviewed at six months. This study showed a temporary improvement in symptoms but with relapse by about six months and was thus reported as a negative trial!

There have been a few other trials. A small trial of Abatacept (which interferes with interactions between white cells) looked at 15 patients with early Sjögren's (disease duration less than 5 years) in an open label study. They found some promising results – the levels of some immunological markers fell and salivary flow rates increased. Another open label study looked at the effects of Belimumab in 30 patients with Sjögren's. Belimumab also reduces the levels of B cells in the blood. The found an improvement on lip biopsy but no change in salivary or tear flow rates.

The JOQUER study looked at the effects of Hydroxychloroquine in a cross over study design (placebo for 6 months followed by Hydroxychloroquine or Hydroxychloroquine followed by Hydroxychloroquine). Interestingly the researchers found not much difference between the two groups at six months but at 12 months the patients who had been taking the active drug for the whole 12 months were better.

In conclusion there are an increasing number of new drugs being trialled in Sjögren's Syndrome. Even though taking part in clinical trials may be of no direct personal benefit the trial may benefit the wider cohort of patients with Sjögren's and increase knowledge of the condition and its treatments so leading to the development of new treatments over time.