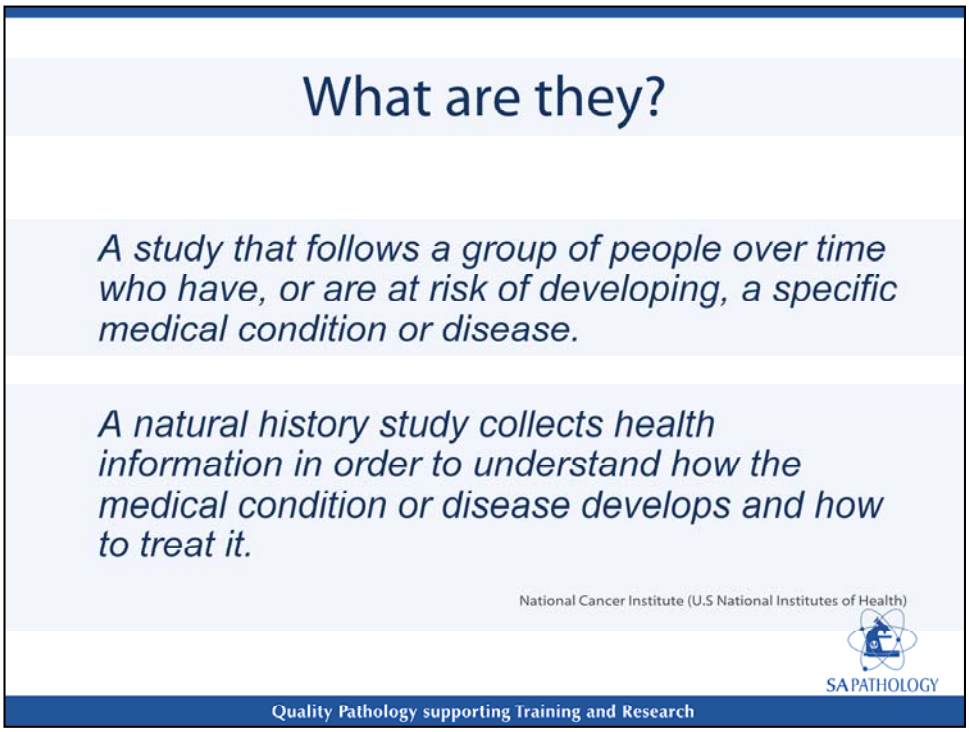
•Would like to thank the organisers for inviting me here today to talk about Natural History Studies and their importance

A brief outline of what I'll be discussing today:



The National Institute of Health definition of Natural History Studies is:

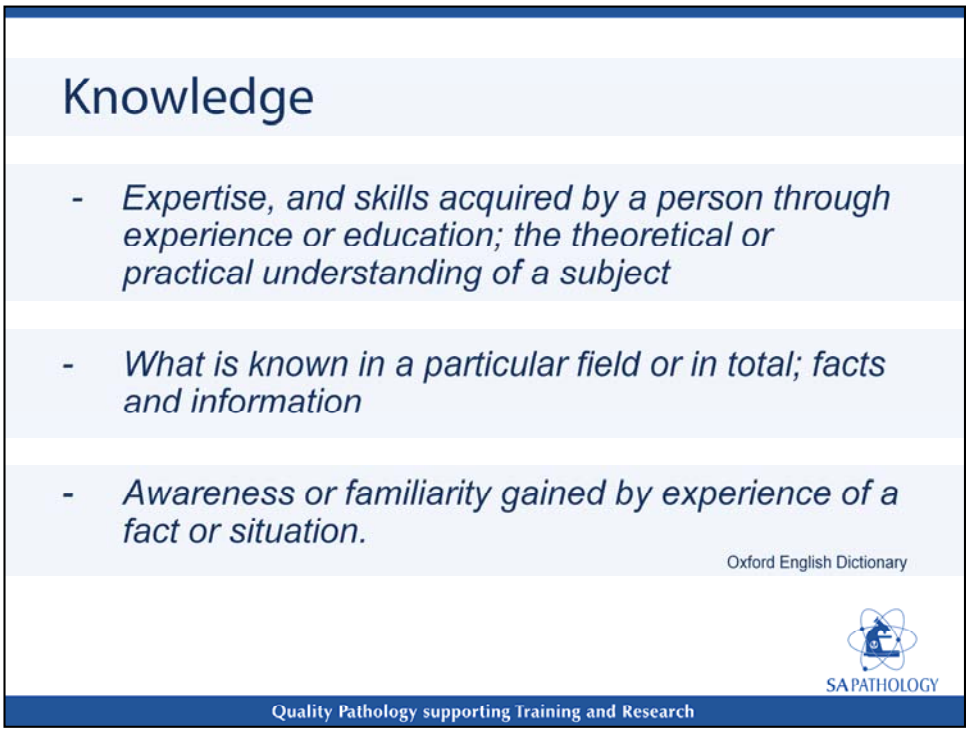
These studies are Observational not experimental

•Interesting… Clinician's and scientists devour this sort of information… for them it is light reading, a coffee table book!

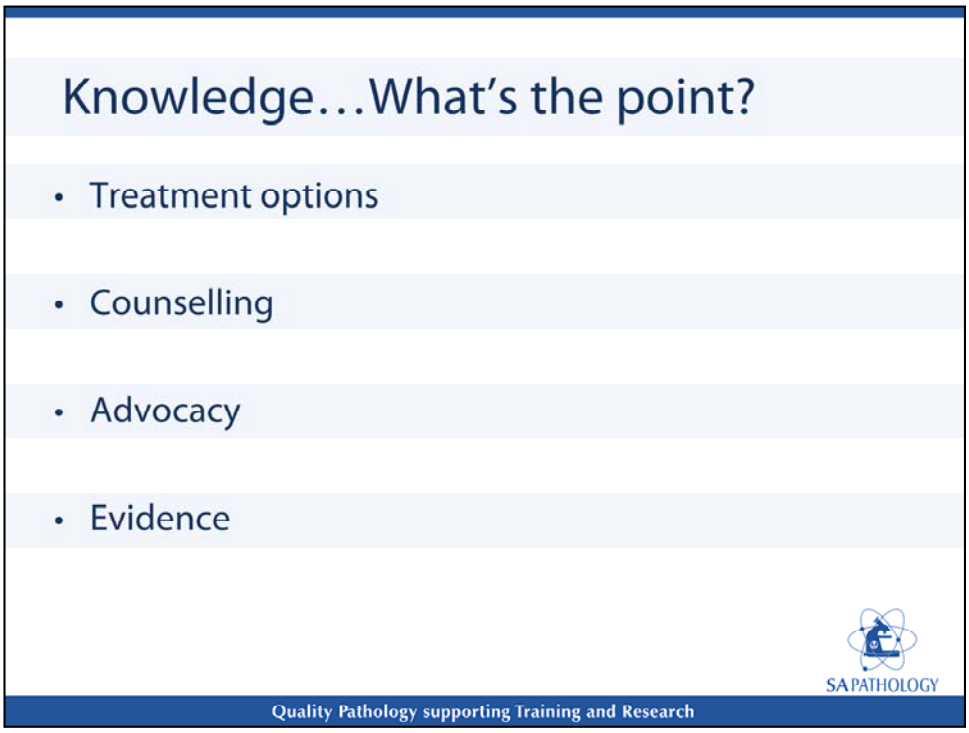
•Is this enough, not really. Why else do we do them

•To increase our knowledge and to assist in clinical trial development.

•I'll discuss these further



•As this is the first time I have spoken in front of a international audience, I decided that to establish some credibility I should provide evidence to support my discussion… And you'll note I've used the Oxford English Dictionary, not Wikipedia… !



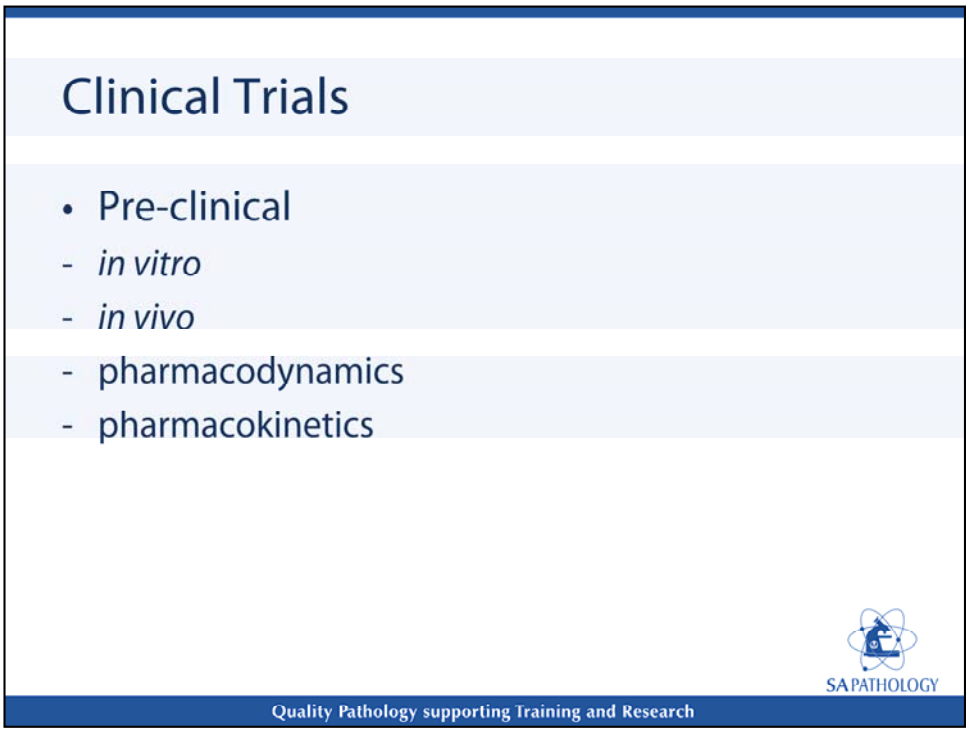
•Greater knowledge and understanding of how MPS affects individuals and their families gives the treating team the ability to optimise patient care and provide appropriate counselling

•Well informed patients, families, clinicians and researchers are more able to advocate both individually and collectively

-Regulatory bodies require evidence to support approval of new therapeutic options

-I could digress here into deep scientific discussion about how increased knowledge can assist to correlate specific genotype with specific symptoms for individuals and how this impacts on treatment options and counselling, but that is a whole session on it's own and much better presented by others with greater scientific knowledge than me.

The fact is, what you really want to hear is how will this actually impact you and your family.



•Designing clinical trials is a really complicated process. Natural History Studies are an incredibly important part of this complicated process

•I'll discuss trials in some more detail to give you an insight into why natural history studies to support them are so important.

• Well before trials are commenced in humans there is much work completed.

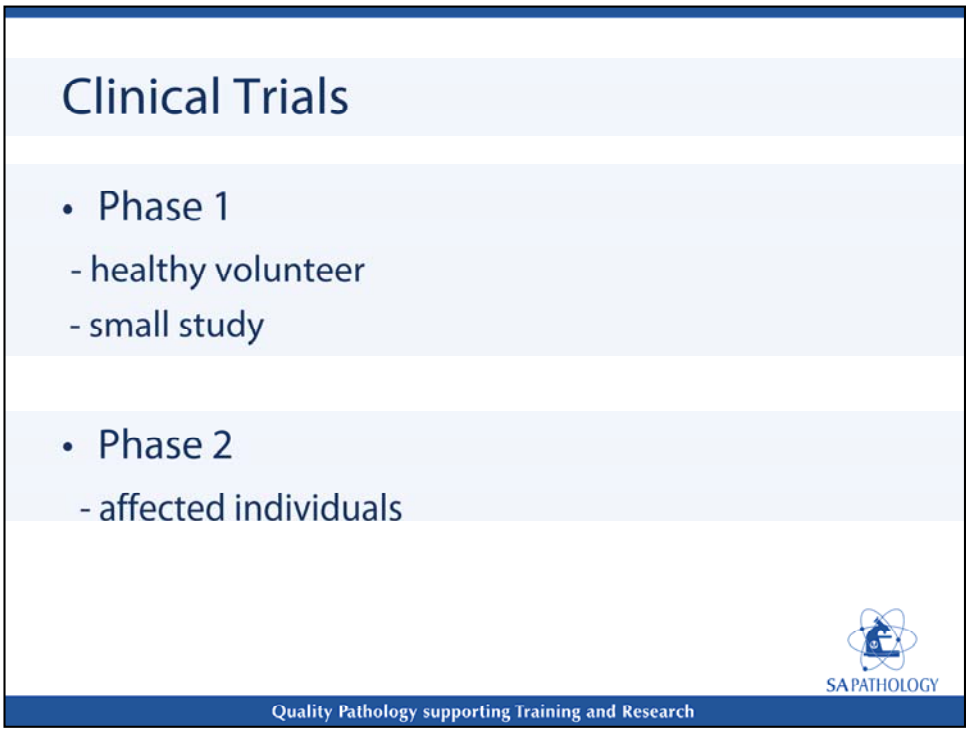
•These pre clinical studies are

•In vitro - test tube

- In vivo - living model

Pharmaco dynamics - effect of drug on body and relationship between concentration and effect

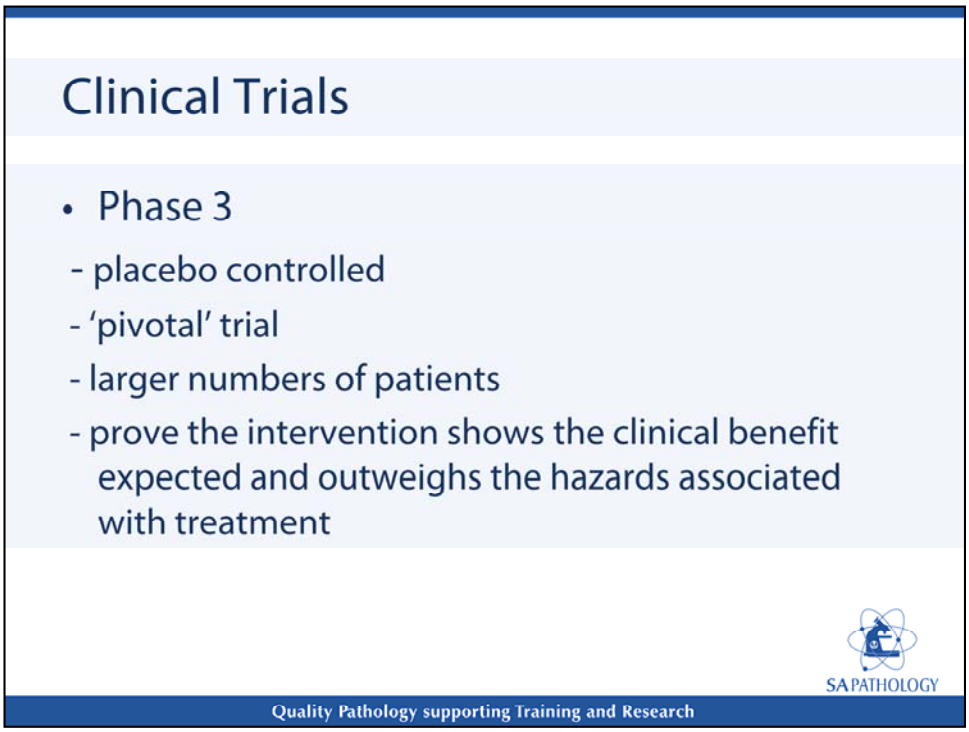
Pharmacokinetics - body's effect on the drug (absorption, distribution, metabolism, excretion)



•Phase 1 and 2 are usually separated, starting with healthy volunteer studies.

•Because MPS conditions are so rare, phase 1 and 2 studies are combined to assess safety and efficacy.

•This is also a good opportunity to discover if the assessments used are actually going to identify the changes we are expecting to see.



Phase 3

Herein lies the most important benefit of Natural History Studies for the mucopolysaccharidoses…

In particular for those who have CNS involvement.

Regulatory bodies need evidence that the treatment improves patient outcome, but without systematic collection and evaluation of what happens without treatment, how can they know?

Placebo control while neurological decline is possible… how can this be justified?? This is why the comprehensive collection of natural history is so important.

•Phase 4 clinical trials can also be used to evaluate therapy on affected individuals who may not fulfill the criteria to participate in earlier phases of clinical trials - for example children under 5 years old. Children under this age are unable to reliably perform the assessments often used in clinical trials.

•Designing trials which satisfy all parties is challenging

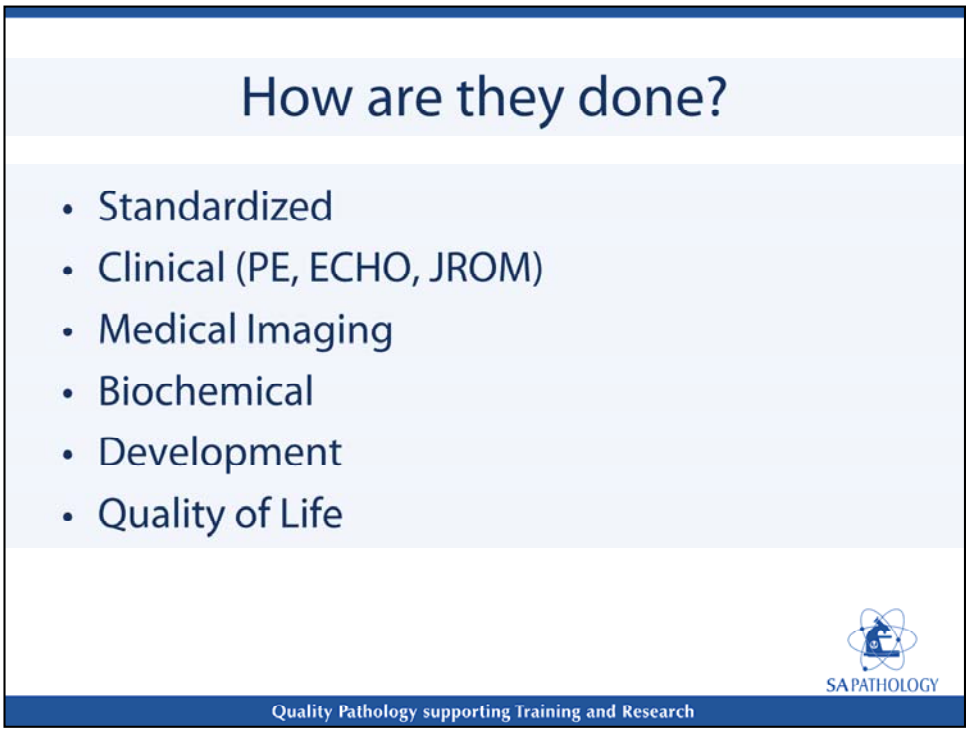
•With more knowledge about individual conditions and the tools required to evaluate these conditions, the better we are able to design trials that lead to faster access to safe and effective treatments.

Natural History studies:

•Gathering good quality natural history information needs to be done in a systematic manner, with large numbers of patients to identify the broad clinical spectrum that these rare disorders display.

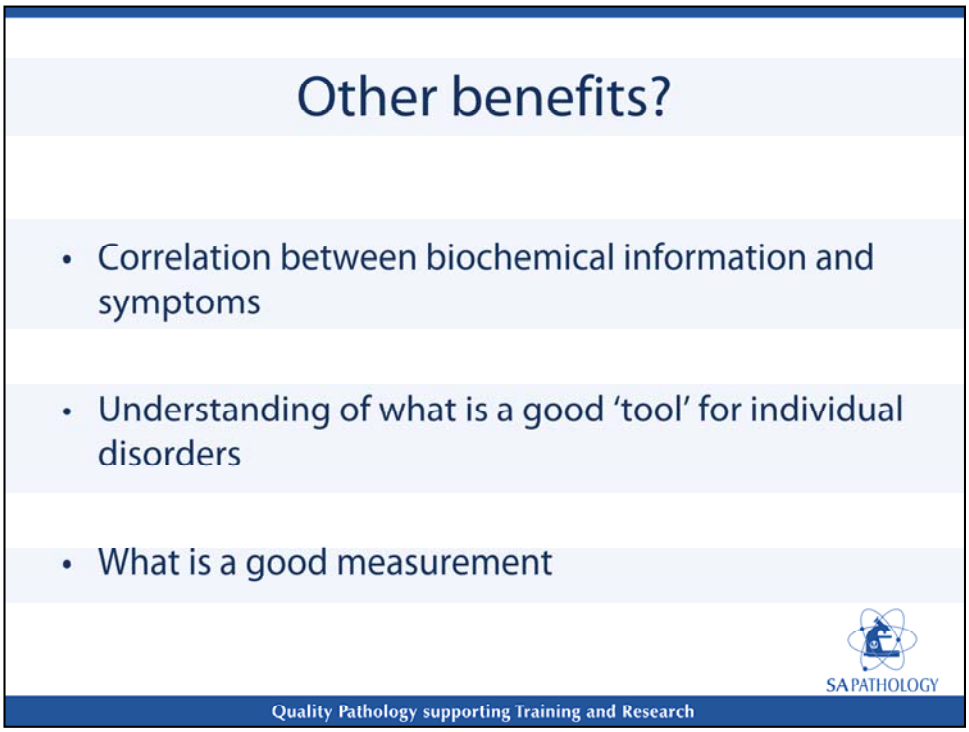
•Given the rarity of the MPS disorders, the only way to do this is with multi-centre studies over extended periods. This provides the chance to collect and document lots of data from lots of patients.

•This also enables us to build a picture of the spectrum of different symptoms and the individuality of symptom progression within each of the disorders.



•There are a large range of different assessments and tests that are performed at multiple time points over the period of the study that are used to establish baselines and track progress of symptoms.

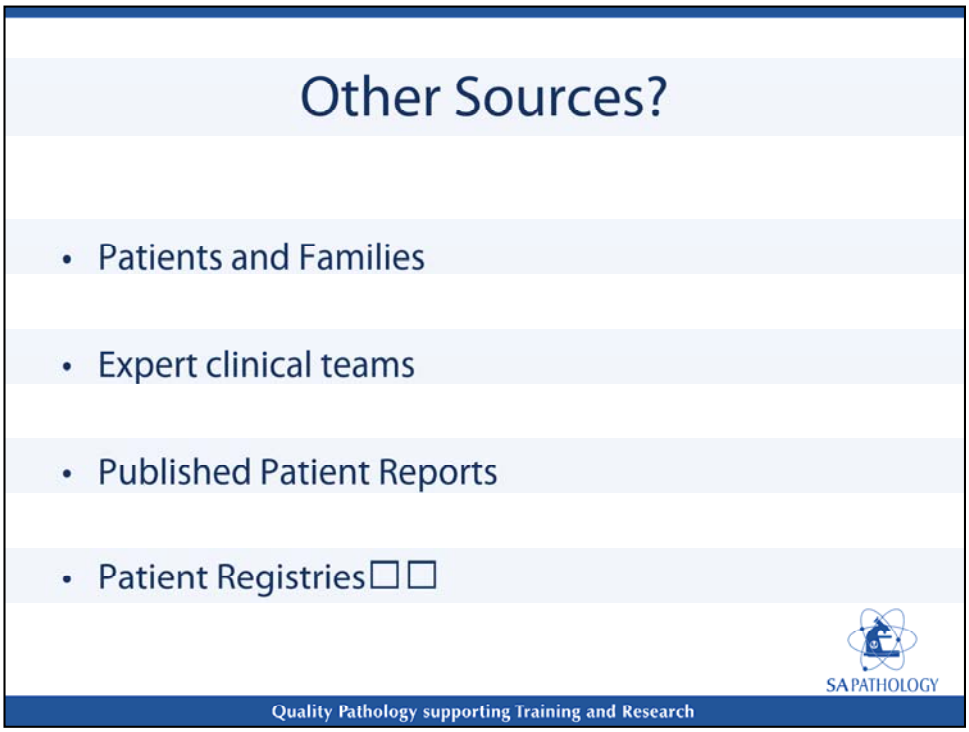
•Natural History studies help us to identify which assessments accurately measure the progression of symptoms in the context of the condition and the clinical significance of the progression.



•There have been many sessions at this conference discussing how we measure particular symptoms and working out how to establish different clinical markers, be they biochemical, imaging, developmental etc, that will better reflect what the symptoms mean to the patient.

• Natural history studies are a way for us to work through these different markers and assess their relevance to the development of symptoms - either for current treatment options, or for predicting rates of likely progression and therefore early intervention treatment options.

•Pharmaceutical Companies can also utilise survey studies and Natural History studies to identify pockets of patients who could potentially participate in clinical trials.



•You may be thinking… there are many sources of Natural History Information.

•Why can't the patient or families' account of the impact of their condition, or the progression of their symptoms be enough? There are very experienced clinicians here in this building.. Surely their expert opinion has an impact

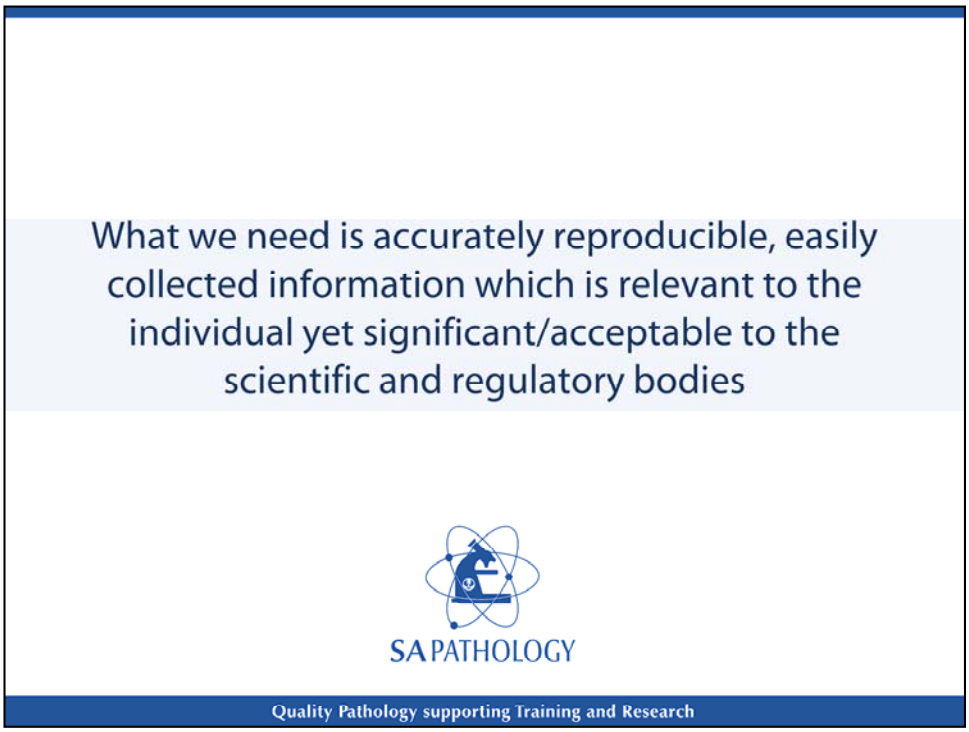
•**The difficulty is that much of this valuable information is not well documented and not collected in a systematic, comprehensive and comparable manner.**

•A number of posters presented at this meeting have opened with "Literature describing..x.. is scarce" and have closed with "Further studies are required…"

•In my research for this talk I came across this quote from Joe Muenzer from 1986: "The management of MPSs can be improved by a better understanding of the natural history of the somatic and central nervous system deterioration in the different disorders. Systematic evaluation and appropriate treatment can lead to an improved quality of life."

•My research - 31 hits on a search for MPS and Natural history - only 18 human, and most with small case report or retrospective medical record review - not systematic, not comprehensive, not consistent and not longitudinal.

•Patient Registries are a source of valuable information.



Any ideas?

Your opinions are invaluable.

What are the aspects of mucopolysaccharidoses that have the most significant impact on you/your child's life?

Thanks

Dr David Ketteridge

Dr Drago Bratkovic

SA PATHOLOGY

Quality Pathology supporting Training and Research