Australian MS Longitudinal Study (past and future) and Primary Progressive MS Study

Aims Australian MS Longitudinal Study

– Set up by Rex Simmons, Canberra Hospital, in 2000/01

– Aims

- o To continue to recruit and **enrol Australian people with MS into the study** and to collect baseline and longitudinal demographic and clinical data on each participant through a self-report questionnaire for the participant and a clinical questionnaire to be completed by the participant's neurologist;

- o To collect and analyse **data on matters of importance to the MS community** through the use of well-designed and ethically approved surveys;

- o To provide **MS researchers** with an established, well-characterised cohort of people with MS for ethically approved, predominantly social-and-applied, collaborative research projects; and

- o To provide data on the issues of practical importance that affect people with MS, their families and carers to MS Australia and the state MS societies to **facilitate the provision of services and advocacy for people with MS.**

Key achievements

– Electricity usage
  o Nice example how actual data can be powerful for advocacy
  o Key finding: People with MS spent ten times as much on air conditioning as the average Australian household.
  o Outcome: Medical electricity rebates negotiated for people with MS in most states

– Health economic surveys
  o Statements on the actual cost of MS have been very useful for advocates, researchers and other people
    • MS costs Australia $1.04 billion a year.
    • Nearly <u>half</u> ($494M) of the total MS cost is due to <u>sickness absence and early retirement</u>.
    • This data resulted in the development of a new project called MS Work Smart, aiming to keep people with MS longer in the workforce and maintaining or increasing productivity:
      – Large cost saving to the society
      – Large benefits to people with MS (socially, financially, personally).

Palmer AJ, et al. The economic impact of multiple sclerosis in Australia in 2010. Mult Scler 2013;19:1640-1646.

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Key achievements

– Employment surveys
  o We obtained Australian data on employment and determined the reasons for leaving employment.
    • Good to have Australian figures
      – 56% of MS patients had lost employment due to MS and 64% were not in the paid labour force.
      – Over 4 years, the longitudinal loss of employment was 5.4%.
    • Useful data for designing interventions
      – The most frequently listed symptoms relating to employment loss were:
        – fatigue (70%), mobility-related symptoms (44%), arm and hand difficulties (39%), and cognitive deficits (37%).
    • Disclosure
      – People who had disclosed their MS status to an employer were more likely to remain in employment!
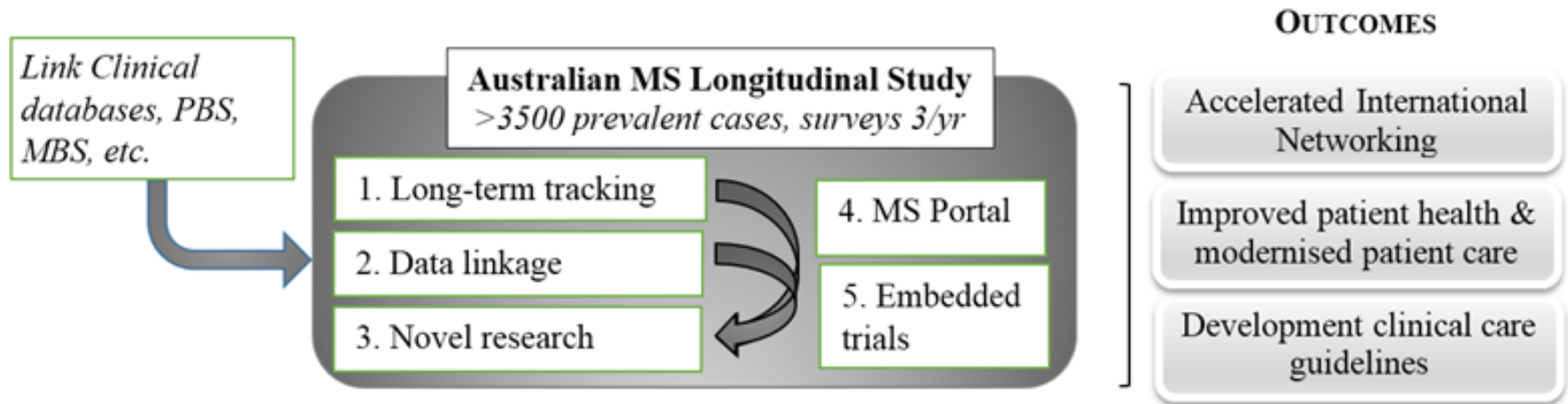
Simmons RD et al. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. J Neurol 2010;257:926-936.

Kirk-Brown A, et al. Disclosure of diagnosis of multiple sclerosis in the workplace positively affects employment status and job tenure. Mult Scler 2013.

http://www.msra.org.au/AMSLS 4

Key achievements

– Employment surveys - Key messages for people with MS

  o The data suggests that many employees with MS are leaving their planning for effective symptom management, and for appropriate accommodations in the workplace, until it is too late.

  o Accessing Employment Services early, via e.g. MS Societies, can be extremely useful. Considering these employment aspects early in the disease process can possibly keep people in the workforce for longer.

  o Those who disclosed their MS to their employer were more likely to be employed longer-term.

  o The majority of employer responses to disclosure are positive and supportive.

  o However, potential discrimination following disclosure may well still occur for a minority of individuals.

Kirk-Brown A, et al. Disclosure of diagnosis of multiple sclerosis in the workplace positively affects employment status and job tenure. Mult Scler 2013.

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New directions

- Five key focuses – see figure

- We will run through each of those five

1. Long-term tracking

Long-term tracking over time - MS outcomes

The aim is to track how people with MS go over time.

Example of what we measure:
- o Disability, patient-reported symptom severity, quality of life, employment outcomes

1. Long-term tracking

Why do we measure this?

1. We can examine factors that are associated with changes over time
   - E.g. Compare disease modifying drugs in relation to employment outcomes and fatigue
   - E.g. examine whether particular lifestyles are associated with better outcomes:
     – Is it the case that those who remain physically active (despite their disability) have a better quality of life?
     – Is it the case that those who follow a particular diet is have a slower progression?
   o It allows for new research questions developed after the data has been collected

2. Data linkage

- **What is data linkage?**
  - Throughout our lives, information is collected about our health and health care. This information is collected by hospitals, health departments and other groups or organisations that provide health services. The collection of this information is usually required by law and is securely stored by the service or agency that collects it.
  - Data linkage is a way of connecting information held by different groups or services in a way that protects a person's privacy. Being able to link data can be very useful in health research including MS. It is cost-effective because we are re-using data that is already collected, and it is non-intrusive because we don't have to obtain already collected information again. Thus, it will create new research opportunities without the need for additional surveys.

- Linking AMSLS data with data from neurologists (MSBase)

- Linking AMSLS data with pharmaceutical (PBS) or Medicare (MBS) use
  - Examining how key clinical disability milestones and treatment decisions affect health service utilisation.
  - Evaluating the short-term and long-term effectiveness of different management decisions in people with MS.
  - Examine use of drugs to reduce specific symptoms and see how that varies by type of MS and disease duration.

3. Novel research

- Employment
  - Monash, Department of Management
    - A/Prof Andrea Kirk-Brown / A/Prof Pieter van Dijk
  - Examine the inter-relationships that impact on the intention to quit.

- Health economic impact
  - Menzies (Prof Andrew Palmer, Prof Bruce Taylor, myself)
  - DEVA project (MSRA, $160,000): Development and Validation of a computer simulation tool to identify interventions and treatments of MS that are excellent value for money.

- Long-term effect of treatment
  - *COMPANZ (*MSRA, $180,000) to compare MS patients from Australia and New Zealand (Prof Bruce Taylor, myself).
  - Comparison of treatments in relation to outcomes such as MS symptoms and employment.

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3. Novel research

- Dental Health
  - University of Queensland, MS Limited
  - Comparison of dental health issues to Australian population.

- Comorbidities in MS
  - Association between comorbidities and health-related quality of life/disability/costs

- Sleep problems
  - Occupational therapist – WA
  - Rate of sleep problems and factors associated with those problems
  - Ultimately: Develop interventions around sleep hygiene, thermo-regulation and relaxation techniques.

4. MS Portal

Vision
- o Create a MS Portal that improves patient care and services.

– Using research data to improve patient care
  - o Allow the participant to share research data (via MS Portal access) with key health professionals such as neurologists.
  - o Visualise data in an easy way
    - • How do outcomes such as quality of life, particular MS symptoms, and disability track over time for a particular person?
    - • How does that compare to other groups of people (all people with MS, people with primary Progressive MS, people with the same disease duration)?
  - o Health professionals might make better decisions to assist people with MS based on this data.

4. Embedded trials

– Improving quality of life through programs that <u>give people with MS new knowledge and skills</u>
  o Better managing fatigue
  o Better lifestyle
  o Better dealing with stress
  o ….

– mstranslate.com.au is a beautiful information resource of scientific information for people with MS, but often more is needed than just information. Just knowing about something, doesn't always mean you know how to change particular aspects of your life.

– The MS Society has great resources/programs available. Often there is insufficient research done to demonstrate that these programs work. I believe we can do far better.

– We could do this research within the AMSLS, because people are tracked over time in terms of their outcomes.

Example: MS WorkSmart

– A remote (e.g. internet) cognitive behavioural therapy program to reduce fatigue and maintain people with MS in the workforce

  o Dropping out of the workforce is a big issue for people with MS (loss of income, reduction and personal identity, etc.)

  o Fatigue is mentioned as the number one factor of why people drop out of work.

  o We will use a remote intervention, so it is accessible for every Australian with MS and it is accessible from their home (no travel required)

  o It focuses on:
    • Energy effectiveness
    • Changing thoughts or core beliefs that are not helpful – cognitive behavioural side…

Example: MS WorkSmart

– It focuses on:
  o Energy effectiveness
  o Changing thoughts or core beliefs that are not helpful – cognitive behavioural side…

The next slide show some examples of things that people have done to reduce their fatigue

I've tried to limit the things I 'must' do in favour of what I want to do

Naps are a daily routine now and useful

I think delegating has helped a lot. Cleaning, cooking, walking dog

Whereas before I was working like an idiot during my good time of the day….I now rest during the morning and am not so tired in the afternoon

I allow myself to rest as soon as needed, then complete my task later

– But quite often there are barriers that sit in the way….

– The next slide show some examples of statements that people made about those thoughts that can sit in the way.

What can get in the way?

*"Resting in the afternoon is **very alien** to me - that's what my granny used to do. **But that's why I end up not being able to do what I want to do"***

*"My **own reluctance** to 'give in' which often results in my overdoing it to the point of inducing severe fatigue which exacerbates other symptoms"*

– This is where the cognitive behavioural approach comes in.

– I will tell you some more about this….

Cognitive behavioural approach

Is concerned with:

– Individuals' attitudes & ways of thinking (that's the **'cognitive'** part)

– what they do (that's the **'behavioural''** bit).

– based on the theory that **cognitions, emotions & behaviours interact** and

that sometimes changing how we think about a situation influences what we feel and what we do.

Back to MS WorkSmart

– So, in MS WorkSmart we will assist you with:
  o Identifying issues that you could improve in relation to fatigue at work (and at home)
  o Identifying barriers that could sit in a way.
  o Trying to overcome these barriers.
  o Assisting you with changing some aspects of your life that will make a difference to you.

– The research bit
  o At the same time, we will measure what you have changed and see whether that resulted in improvements in your fatigue and important aspects of your working life.
  o We would like to see the evidence that this actually works, otherwise there is no point of doing these type of programs.
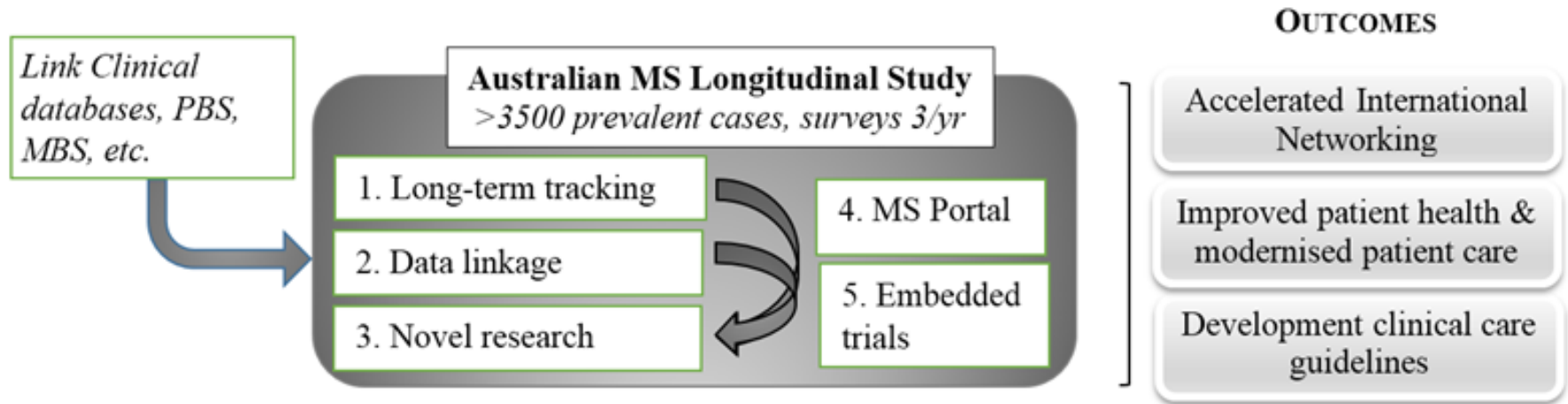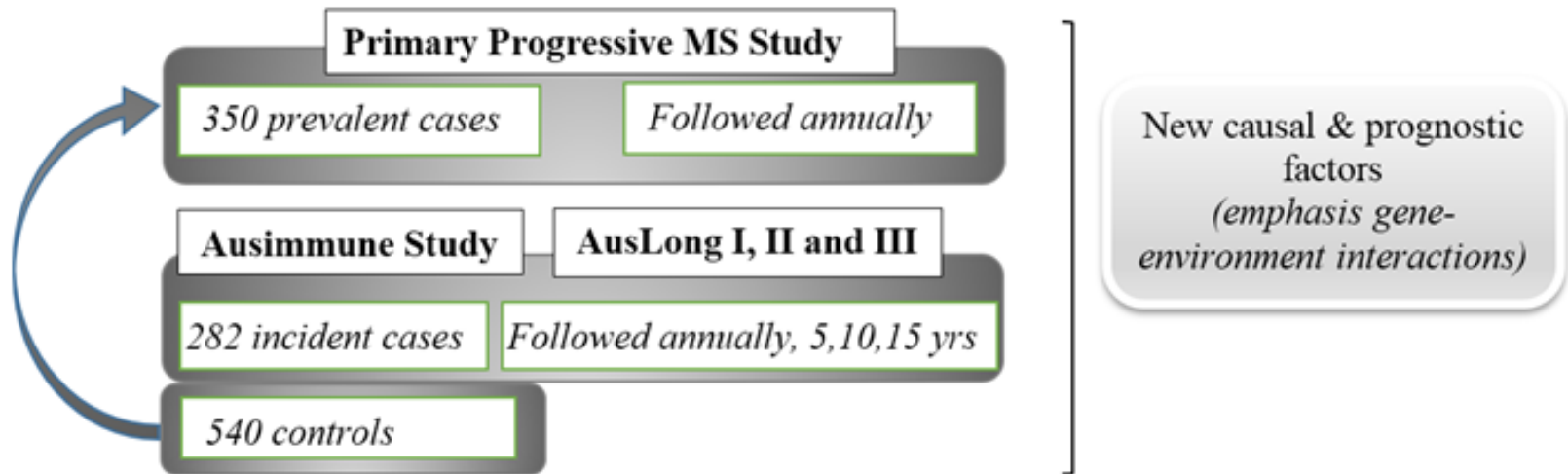
Okay, I think that is enough about the AMSLS study.

I will now shift gears to do primary Progressive MS study.

Primary Progressive MS study

Primary Progressive MS Study

350 prevalent cases   Followed annually

Ausimmune Study   **AusLong I, II and III**

282 incident cases   Followed annually, 5,10,15 yrs

540 controls

New causal & prognostic factors
(emphasis gene-environment interactions)

– Case-control study:

A little bit of background knowledge:

– Case-control study
  - A study where we look at factors that influence <u>the onset of MS</u>
  - We ask about factors that happened before the onset
  - We compare people with MS to people without MS
  - Type of people with MS
    - Prevalent cases: anybody with established MS
    - Incident cases: newly diagnosed people with MS

– Longitudinal study
  - A study where we look at factors that influence the progression of MS
  - We ask about factors that happen during the disease
  - We compare people in relation to outcomes such as disability progression, symptom severity and quality of life

– First I will tell you a little bit more about why we want to look at this and about the differences between Primary Progressive MS and bout onset MS (relapsing remitting MS)…

Why?

– Large number of treatments for people with RRMS

– Currently no treatments for people with progressive MS!

– International call for research into Progressive MS (Progressive MS Alliance)

Differences PPMS vs bout onset

– Treatment response

o Disease modifying therapies seem to work for people with bout onset MS but not for those with progressive MS.

– Pathology

o Differences more quantitative rather than qualitative

– Epidemiology

o Sex ratio closer to 1

- Maybe the protective effect of parity is less important?

o Latitudinal gradient nearly absent

- Maybe sun exposure / vitamin D are less important?

o Presentation at onset

- Motor symptoms more common in PPMS, while sensory or visual symptoms less common

o Onset later (around 9 years)

o Progression faster

- reach EDSS milestones of 4.0, 6.0 and 8.0 more rapidly

o *HLA-DR15* genotype similar

o 110 susceptibility genes similarly distributed

Our previous epidemiological studies

Major findings

- Tasmanian MS case-control study
  - Identified sun exposure as a novel risk factor (2003)
  - Identified sibling exposure (measure of infection load) as a novel risk factor + interaction with *HLA-DR15 (2005, 2010)*
- *Ausimmune study*
  - Identified parity (having more children) as a novel protective factor (2012)
  - Found that both sun and vitamin D levels were important (2010)
  - EBV viral load was not an important risk factor (2010)
  - Found that the known key risk factors can explain about 64% of MS (2015)
- Tasmanian MS Longitudinal study
  - Low vitamin D associated with relapses (2010) – resulted in major clinical trials.
  - Smoking associated with clinical course (2009)
  - Identification of interactions between genes and environmental factors (vitamin D pathway genes)
  - Lipid profile associated with disability (2015)

But….

Sub-group analysis for PPMS not possible as only 10% of people had PPMS

Therefore a need to have studies that solely focus on PPMS!!!

Prevalent case-control study (funded MS Research Australia)

- o Recruit 350 cases with PPMS
- o Collect same data as Ausimmune study (an incident case-control study)case-control
- o Use control data (n=540) from Ausimmune study
- o Hypotheses
  - Established risk factors in MS, including low sun exposure, infectious mononucleosis, smoking, high antibody levels to the Epstein-Barr virus *HLA-DR15* genotype are associated with an increased risk of PPMS onset.
  - Low parity, lack of younger sibling exposure and exposure to livestock are associated with an increased risk of PPMS.

PPMS Study – Phase 1

What do we measure?

- o In an interview by phone we will ask about chemical exposure, how many siblings you've had, time you spent outside at different age periods, illnesses that you've had, smoking history, etc.
- o We also use a calendar to measure particular things about people's lives.
- o We asked people to go to a local pathology for a blood sample in which we can measure for example antibody levels to viruses and vitamin D levels, and obtain genetic information.
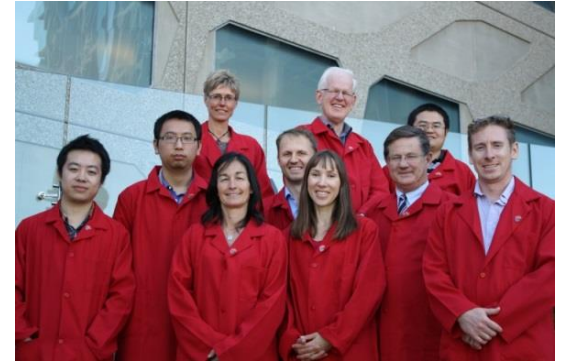
PPMS Study – Phase 2

Longitudinal study of PPMS

– Follow these people over time using the AMSLS

– Examine factors that influence the progression of people with PPMS

– Mostly using online surveys

We hope to unravel some of the pieces of the puzzle of primary progressive MS!

Thank you

Australian MS longitudinal study:
Web-link: http://www.msra.org.au/AMSLS
Email: AMSLS.info@utas.edu.au

PPMS study:
Web-link: http://www.menzies.utas.edu.au/ppms
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