Developing a Clinical Research Programme

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UCD School of Medicine & Medical Science

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Scoil an Leighis agus Eolaíocht An Leighis UCD

Disclosures

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ViiV Healthcare, Merck Sharpe and Dohme, Gilead, Janssen Cilag (Tibotec), Bristol Myers Squibb

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- Merck Sharpe and Dohme
- Science Foundation Ireland
- Health Research Board (Ireland)
- Molecular Medicine Ireland
- Wellcome Trust
- NIH


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My environment……

Mater Misericordiae University Hospital (MMUH)

What is going on in our department?

- How many PLWH in the clinic?
- Who are these PLWH?
- How many are on treatment?
- Which treatments?
- What is heppening to them?

….who cares?

Establishing research….

There are two types of people!

‘Mmmmm…I don’t think you can’t do that….!’

Establishing research….

‘Yes we can!’

The MMUH ID Cohort

Mater Misericordiae University Hospital (MMUH)

'Create a brand!'

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Misericordia

Steps to becoming an investigator….

1. Build up your c.v. – publications / presentations
2. Develop a broad area of expertise
3. Develop a track record
4. Co-applicant on research grants
5. Seek ‘soft’ money –
   - Scholarships
   - Institutional grants
   - Pharmaceutical funding
6. Fellowship or new investigator grants (supervisor)
7. Project grants (P.I.) / Large Pharma awards
   - Demonstrate ability to supervise (MD / PhD)
   - Develop collaborations / establish research team
8. Programme grants (P.I.)

What is going on in our department?

- How many PLWH in the clinic?
- Who are these PLWH?
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- Which treatments?
- What is heppening to them?

….who cares?

What do I need to answer my questions?

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DATA!

Institutional grant

Alan Macken

Data Manager, HMRG

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…..from County Mayo!

Why you don't want to be from Mayo…..

Why utilise routine clinical data?

- Enhances patient care
  - Audit
  - Access to therapies – feasibility for clinical trials
- So that you can record what you're doing!!
- Builds research capacity / expertise
  - Basis for funding applications
- Streamlines research
  - One protocol covers all analyses / audits
  - Avoids unnecessary duplication of effort
- Enables collaboration

Conducting local research

- Access to appropriate patient population
- Have a good data collection tool
- Get appropriate approvals
- Store samples
- Motivating colleagues to do research (share the workload)
- Exploit available data sources
- Sharing data and getting results

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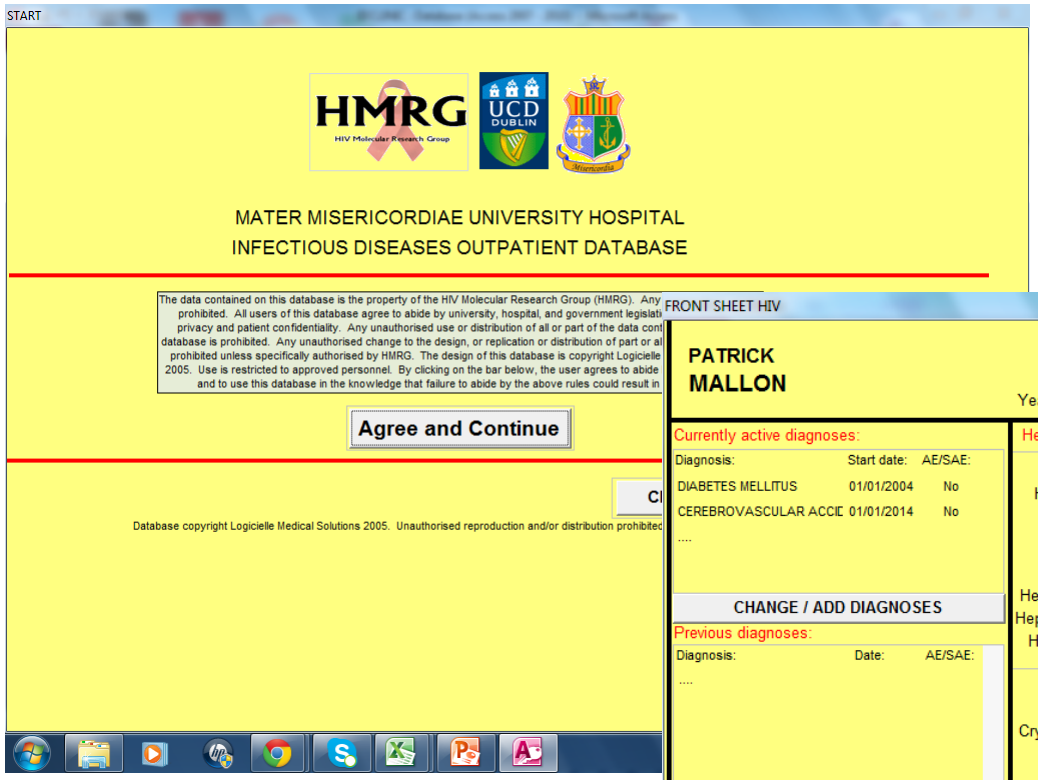
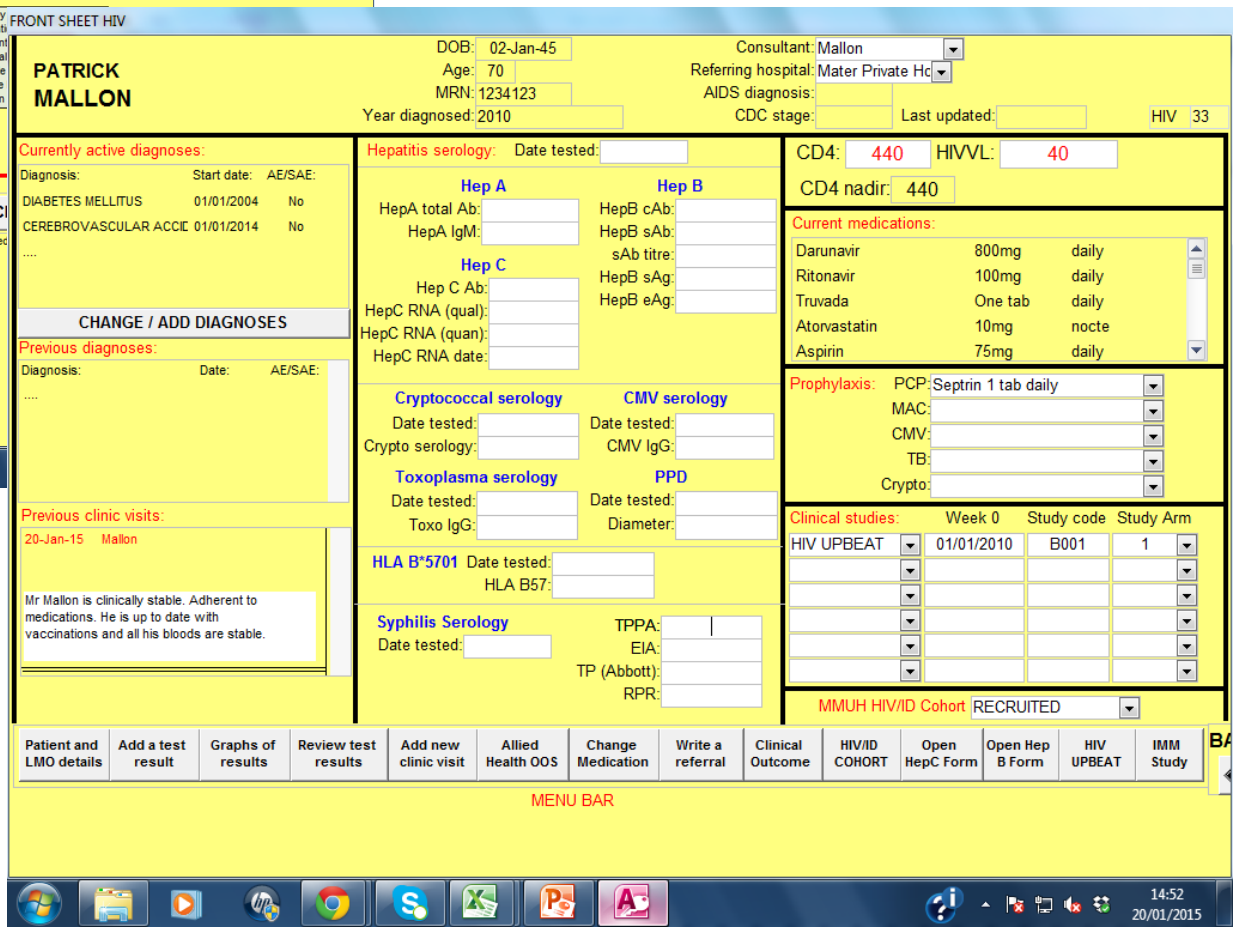
Electronic records and research





>1,700 subjects recruited

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Approvals

- Study Protocol
  - Details the process for enrolment
- Keep the protocol broad – avoid specifics
  - e.g. young people with HIV rather than adolescents
  - Avoid too many restrictions to recruitment
  - Consider wider group outside of HIV? (controls)
- Get the appropriate regulatory approvals
  - Ethics committee
  - National regulatory bodies
- Request approval for collection of all ‘routine’ clinical data
  - Blood results
  - Investigations
  - Medical history

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Storing samples

- When designing cohort think of what you want to do, not what you currently can do – aspirations
- Storage of samples facilitates translational research
- Serum, plasma, DNA
  - Preferably fasting – standardise
- Build into original consent (? Optional)
- Use of plasma / serum for biomarkers
  - Usually straight forward approval
- Use of DNA for research
  - Consider local regulations around use of DNA
  - Host versus pathogen analyses

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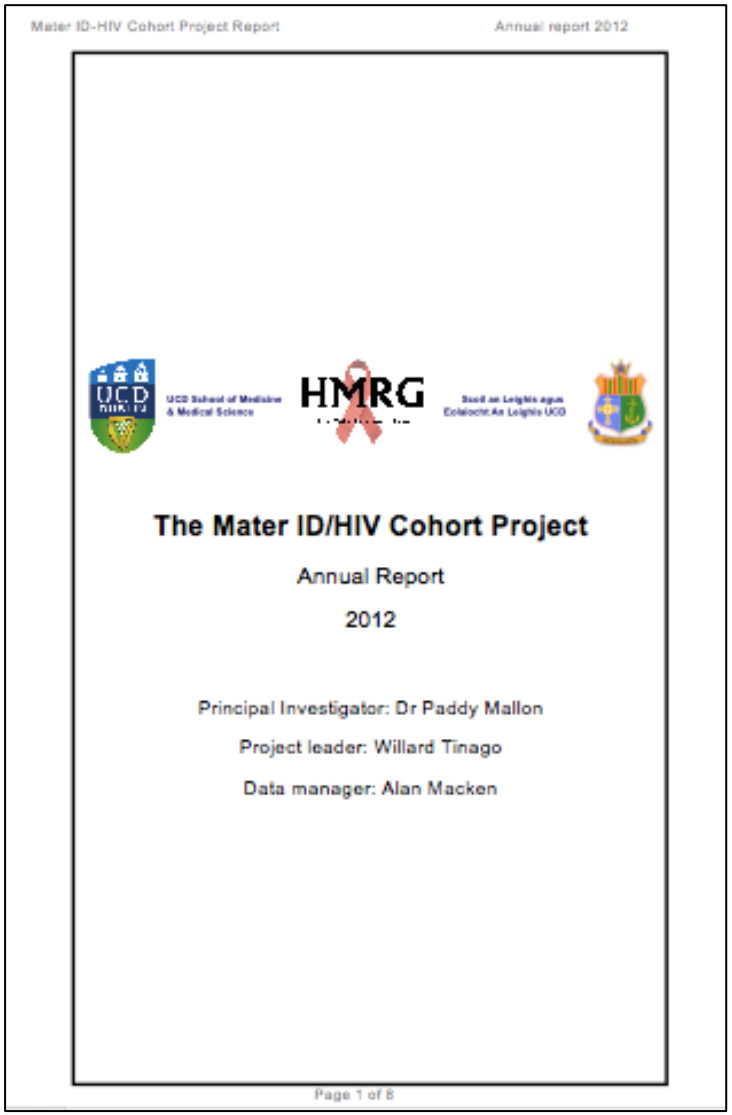
Incentivise Data Collection

- Database utility to make clinical work easier
  - Clinical summaries
  - Access to results (graphs)
  - Automated letters
- Build in competition to data collection
  - Competitive recruitment
  - Awards / recognition for recruitment
- Regular communication maintains momentum
  - Updates on cohort statistics
  - Quarterly / Annual reports
  - Highlight dissemination (abstracts / manuscripts)

Communication

- Weekly updates from data manager
- Clinic-based recruitment figures
- Monthly recruitment figures
- Milestones celebrated
- Annual report to all stakeholders

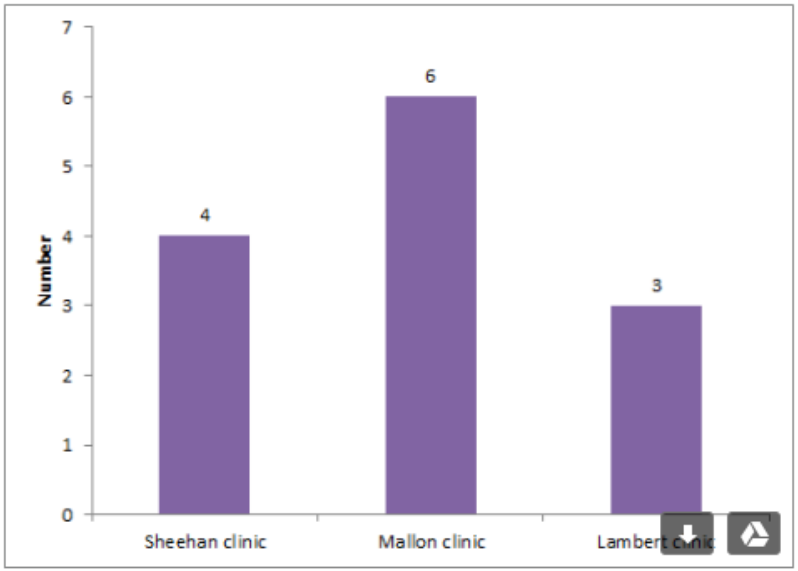


Communication

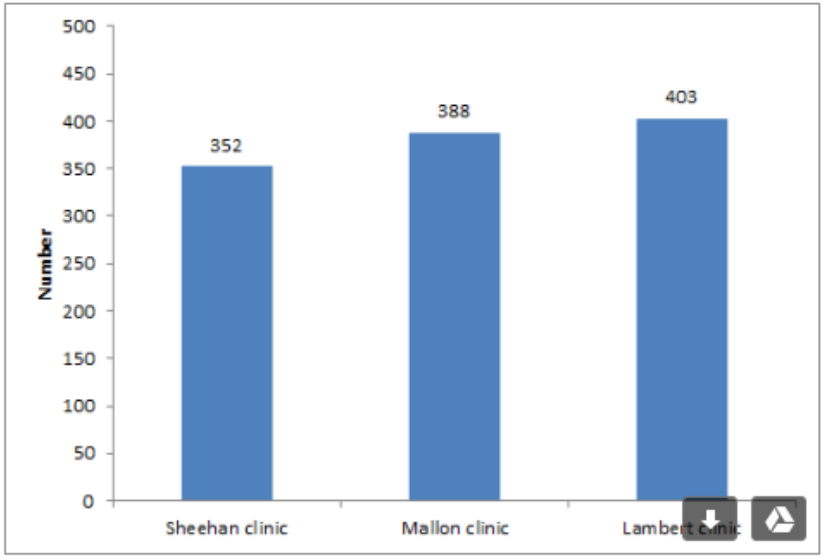
Well done team, what a milestone! **1001** recruited and still counting.....

Thank you for the continued support with recruitment for the Mater ID Cohort.

Last week recruitment statistics.



Overall recruitment by clinic since 2013.



Conducting local research

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- Exploit available data sources
- Sharing data and getting results

Exploit available data sources

- Look around for data linkages
- Can save time +++
- Explore opportunities for direct linkage with other databases
  - Laboratory
  - Pharmacy / drug dispensing
  - Government records (deaths)
- Data linkages can be real-time or ‘data dumps’
- Consider a ‘Source Data Agreement’ - GCP

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Sharing data and getting results!

- Develop protocol for sharing data
- Ensure the data is used according to ethics / regulatory approval
  - Important if external requests
- Ensure confidentiality is maintained
  - Emails / print outs
  - Memory sticks
- Ensure you are credited for data collection
  - Clear authorship policy
  - Funding
- Keeps everyone happy!

Clinical, immunological and treatment-related factors associated with normalization of CD4+/CD8+ T-cell ratio: effects of naïve and memory T-cell subsets

Tinago W[1], Coghlan E[1], Macken A[1], McAndrews J[2], Doak B,[2] Fuller-Prior C[2], Lambert J[1,3], Sheehan G[1,3], Mallon P[1,3]

[1]HIV Molecular Research Group, School of Medicine and Medical Sciences, University College Dublin, Ireland
[2]Department of Immunology, Mater Misericordiae University Hospital, Dublin, Ireland
[3]Department of Infections Diseases, Mater Misericordiae University Hospital, Dublin, Ireland

PLOS ONE May 9 2014; 9(5):e97011

The Mater Immunology Study

1. We thought of a research question
2. We explored what collaborations would be required:
   - Immunology Laboratory
   - External advice (Sydney)
3. We explored feasibility - single clinic
4. We sought funding - €10k local pharma
5. We presented and discussed results
   - Spanish cohort

The Mater Immunology Study

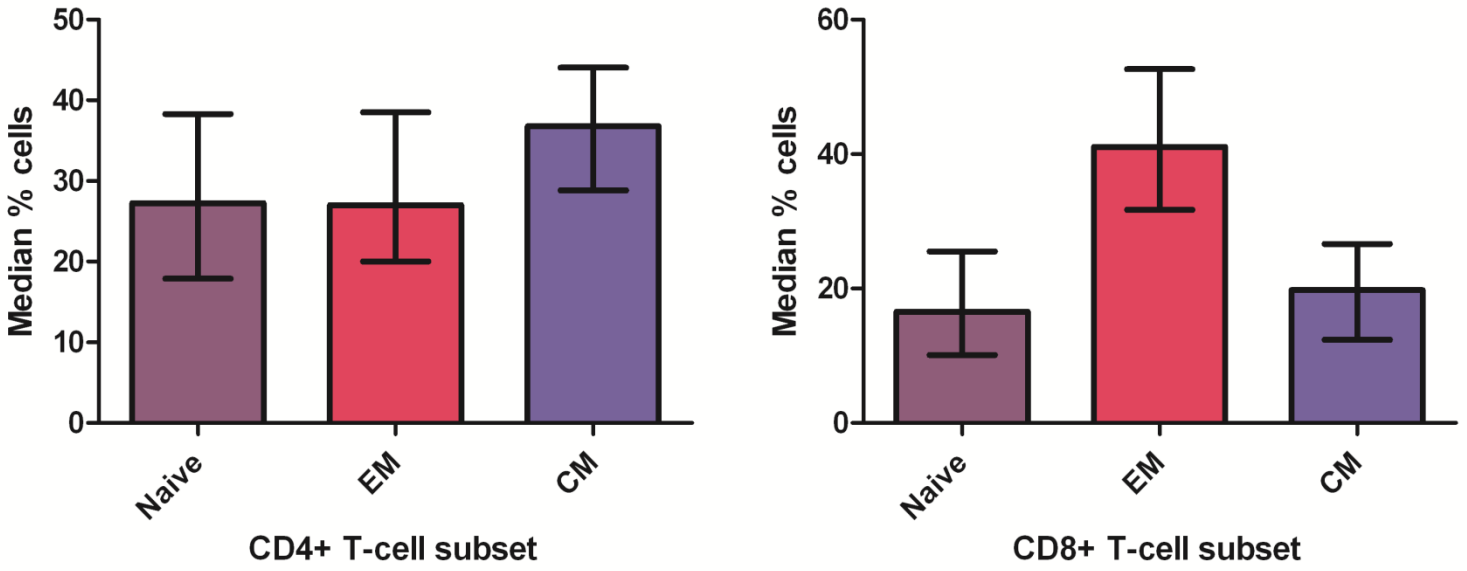
- Prospective cohort on ambulatory HIV+ patients attending MMUH ID clinics
- N=190 adults, 42 (36-48) yrs old, 64% male, 65% Caucasian
- CD4+ and CD8+ T-cell subsets:
  - Naïve cells CD45RO-,CD62L+
  - Central memory cells CD45RO+,CD62L+
  - Revertant memory cells CD45RO-, CD62L-
  - Effector memory cells CD45RO+CD62L-

Tinago W. et al. PLOS ONE May 9 2014; 9(5):e97011

The Mater Immunology Study

- CD4+/CD8+ T-cell ratio 0.6 (0.4-1.0)
- CD4+/CD8+ T-cell ratio≥1 50/190 (26.3 %)

Figure 2. Distribution of CD4+ and CD8+ expanded T-cell subsets



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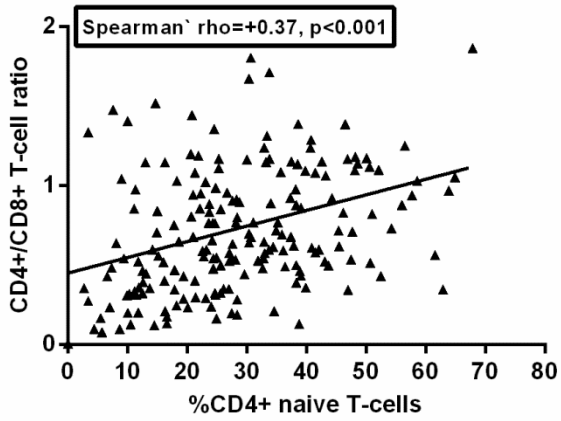
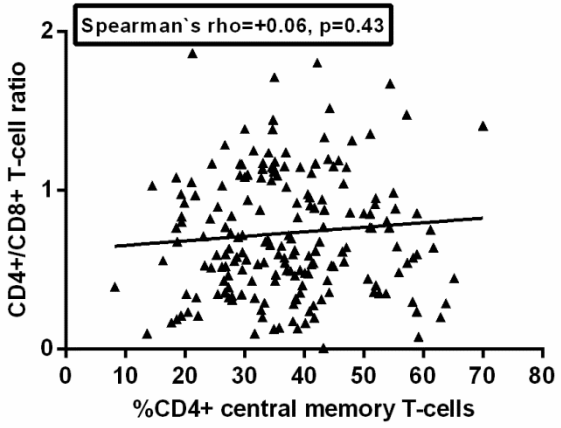
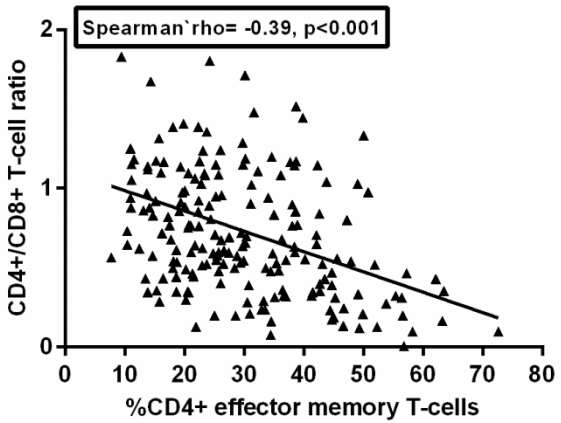
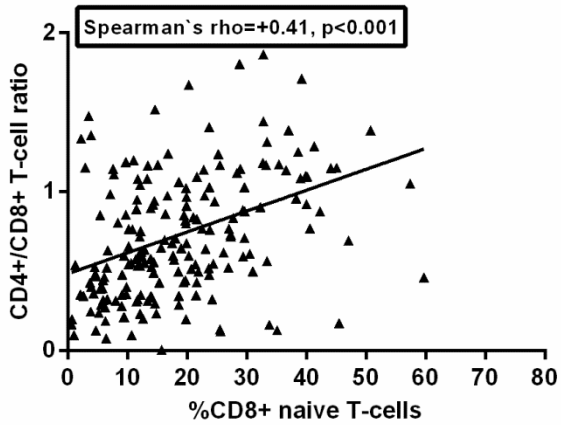
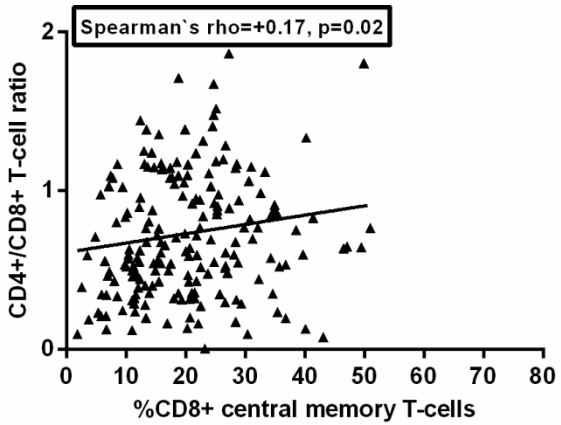
The Mater Immunology Study

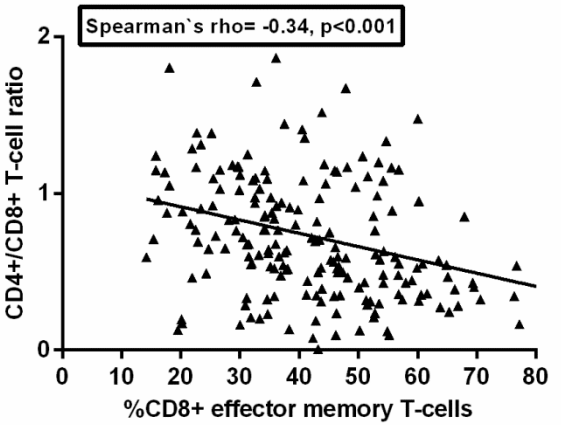












Tinago W. et al. PLOS ONE May 9 2014; 9(5):e97011

The Mater Immunology Study

	†All patients (N=190)			¥Patients on ART with HIV RNA<40cp/ml (N=149)		
	Coefficient	95% Confidence Interval	P-value	Coefficient	95% Confidence Interval	P-value
Total cumulative ART exposure (years)	+0.014	0.0042, 0.025	0.006	+0.014	0.0022, 0.026	0.021
Nadir CD4+ T-cell count (per 10cells/mm^3 increase)	+0.011	0.0081, 0.014	<0.001	+0.013	0.0084, 0.017	<0.001
Absolute CD8+ T-cell count (per 10cells/mm^3 increase)	-0.0044	-0.0056, -0.0033	<0.001	-0.0052	-0.0068, -0.0036	<0.001
%CD4+ effector memory (CD45RO+CD62L-)	-0.0036	0.0074, 0.00006	0.054	-0.0057	-0.010, -0.0012	0.014
%CD8+ naive (CD45RO-CD62L+)	+0.0088	0.0044, 0.013	<0.001	+0.0080	0.0028, 0.013	0.003

†Adjusted for age, gender, ethnicity, Hepatitis C status, and HIV RNA,

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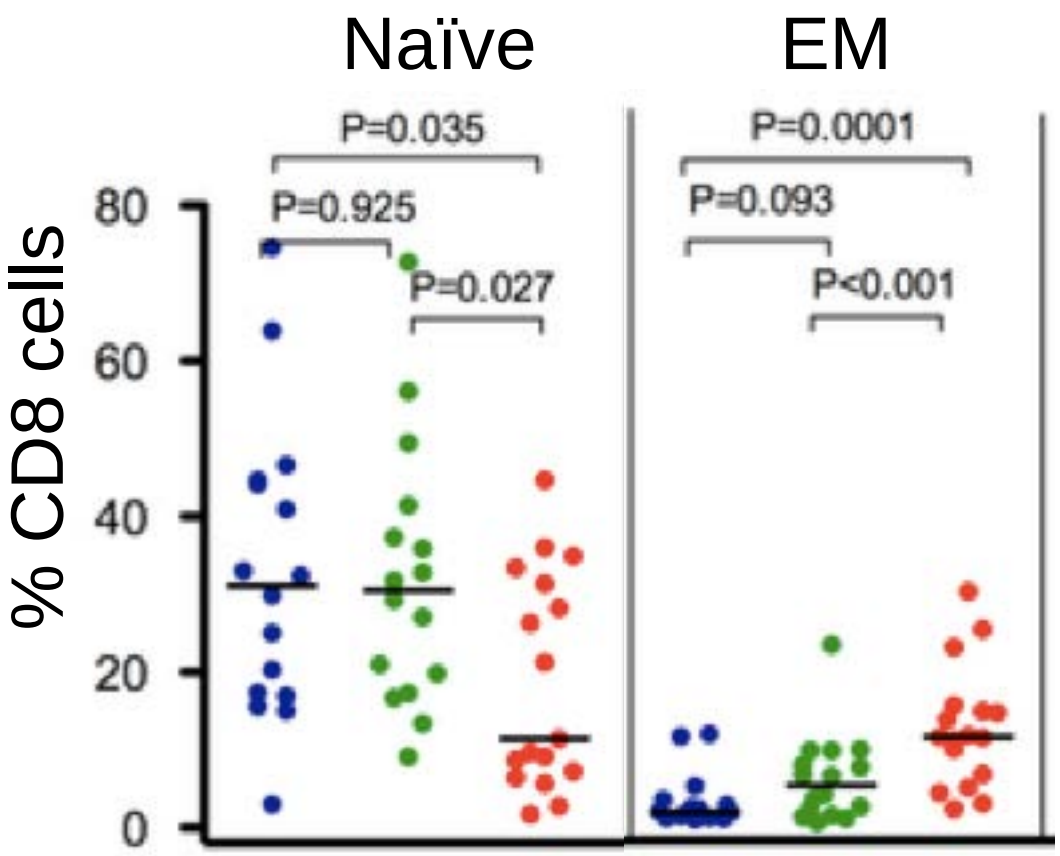
NB: Coefficients of %CD4+, %CD8+ T-cells and their subsets are per 1% increase

Tinago W. et al. PLOS ONE May 9 2014; 9(5):e97011

CD4:CD8 Ratio – naïve CD8+ T-cells



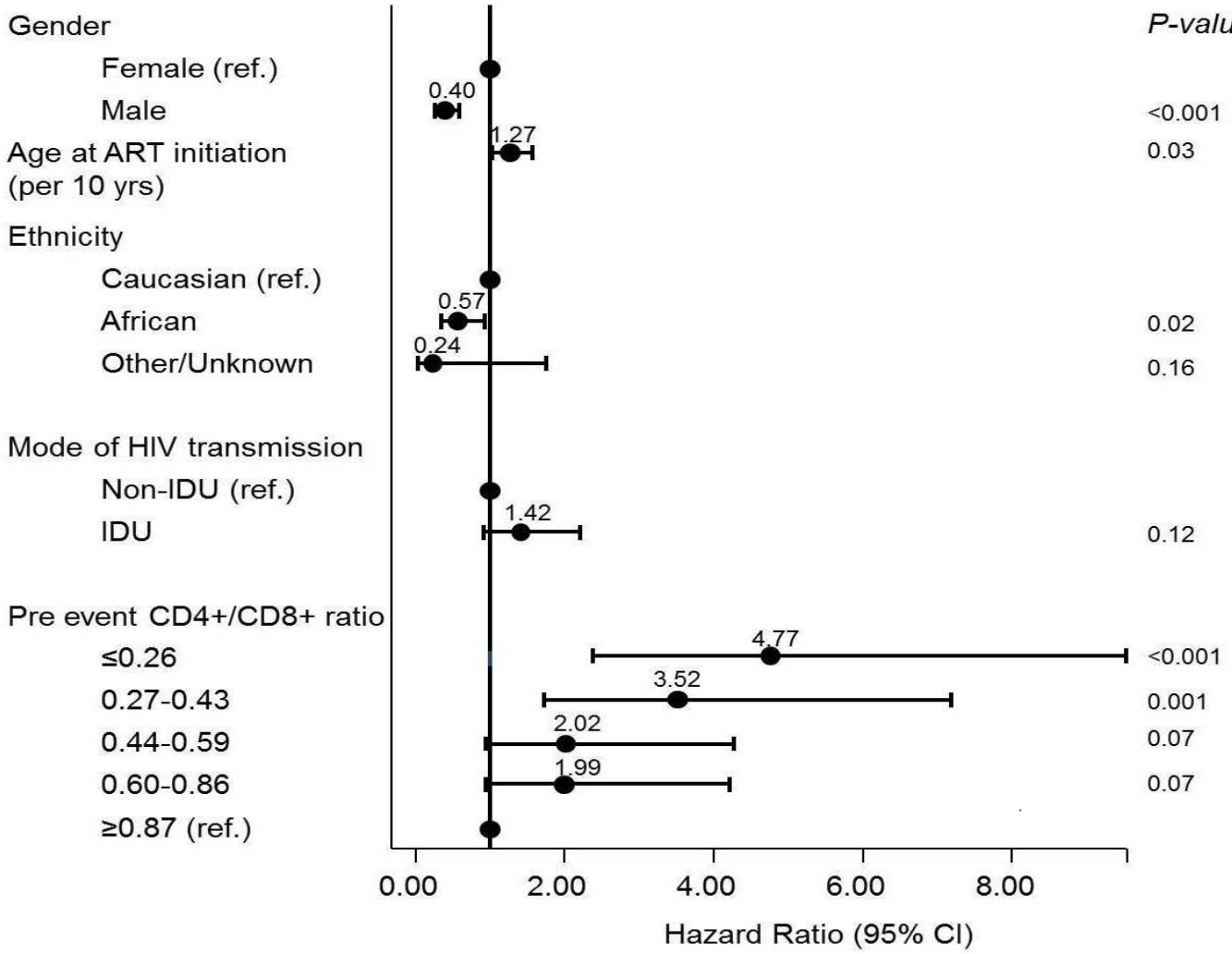
HIV-
HIV+ CD4>500 **CD4:CD8>1**
HIV+ CD4>500 **CD4:CD8<0.4**

- Each 10% decrease in the CD4/CD8 ratio and each 10% increase in the CD8+ T cell count associated with 48% and 22% higher odds of serious non-AIDS events, respectively.

Serrano-Villar S et al. PLoS Pathog 2014:10(5): e1004078. doi:10.1371/journal.ppat.1004078

Biomarkers and outcome – CD4:CD8 ratio

Non-AIDS event[4]
(HR, 95% CI)



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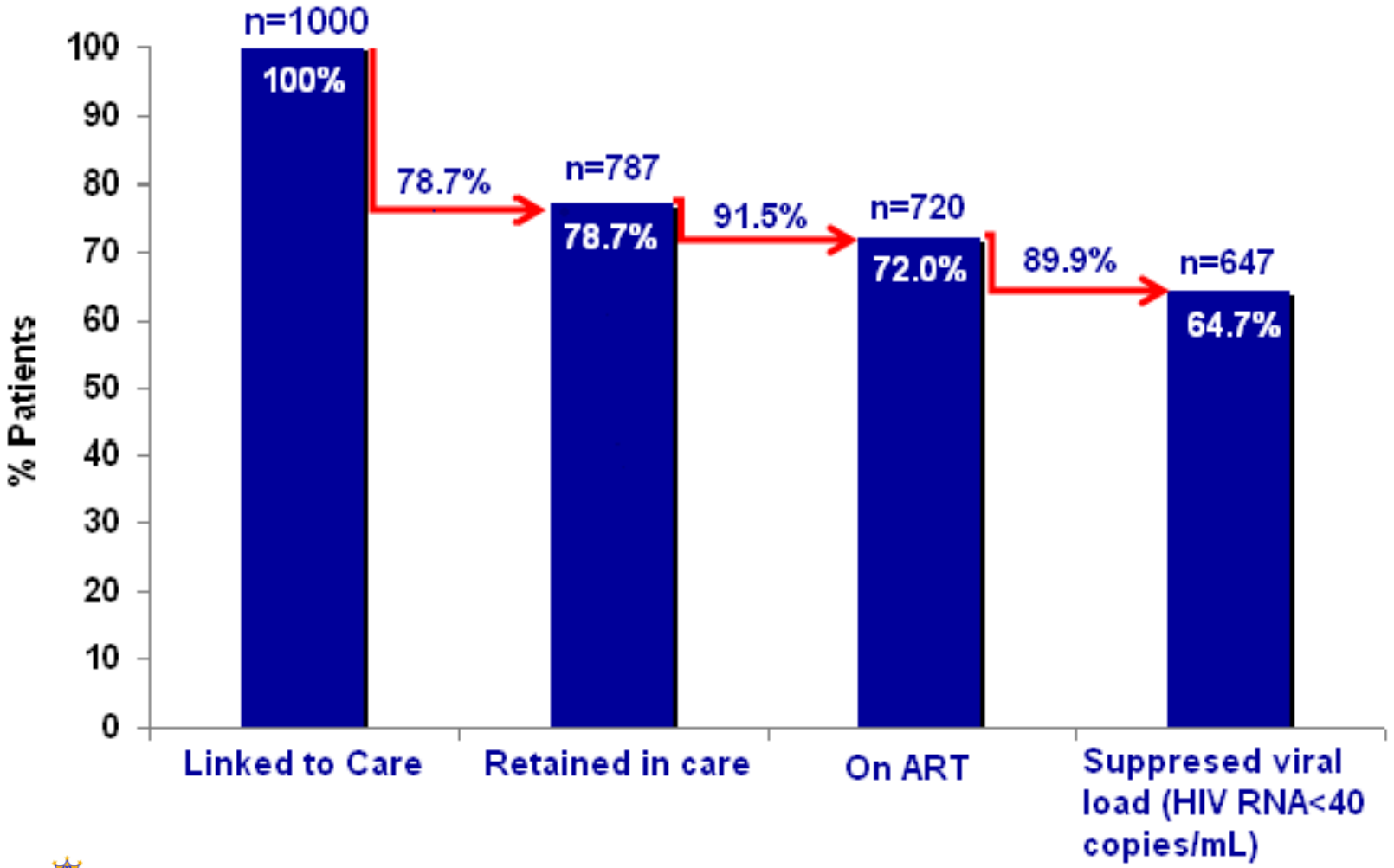
McGettrick P et al. CROI 2016 Abstract 710

HIV care continuum – Ireland



McGetterick et al. HIV Clin Trials. 2017 May;18(3):93-99

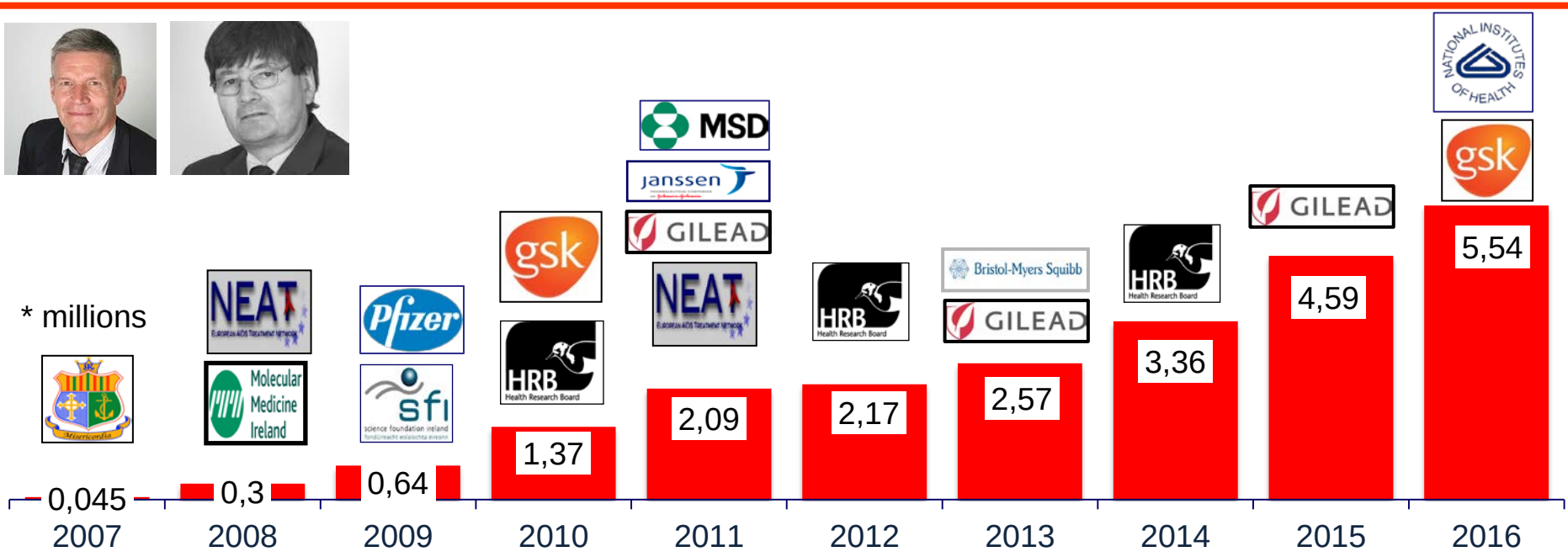
The Mater ID Cohort

- Modified consent to collect viable PBMC
- Flu immunology analysis
- Spinal infection case series
- Viral hepatitis
- Prevention Support Service research

Cohorts……..

- Putting thought into the design of a cohort study can maximise research opportunities
- Database tool is only one component
- Always think into the future
- Seek consent
- Standardised processes essential
- Always look for opportunities to **collaborate**

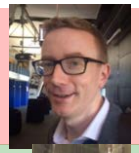
Building research – people & funding

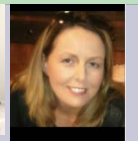


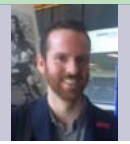
Clinical

Non-clinical

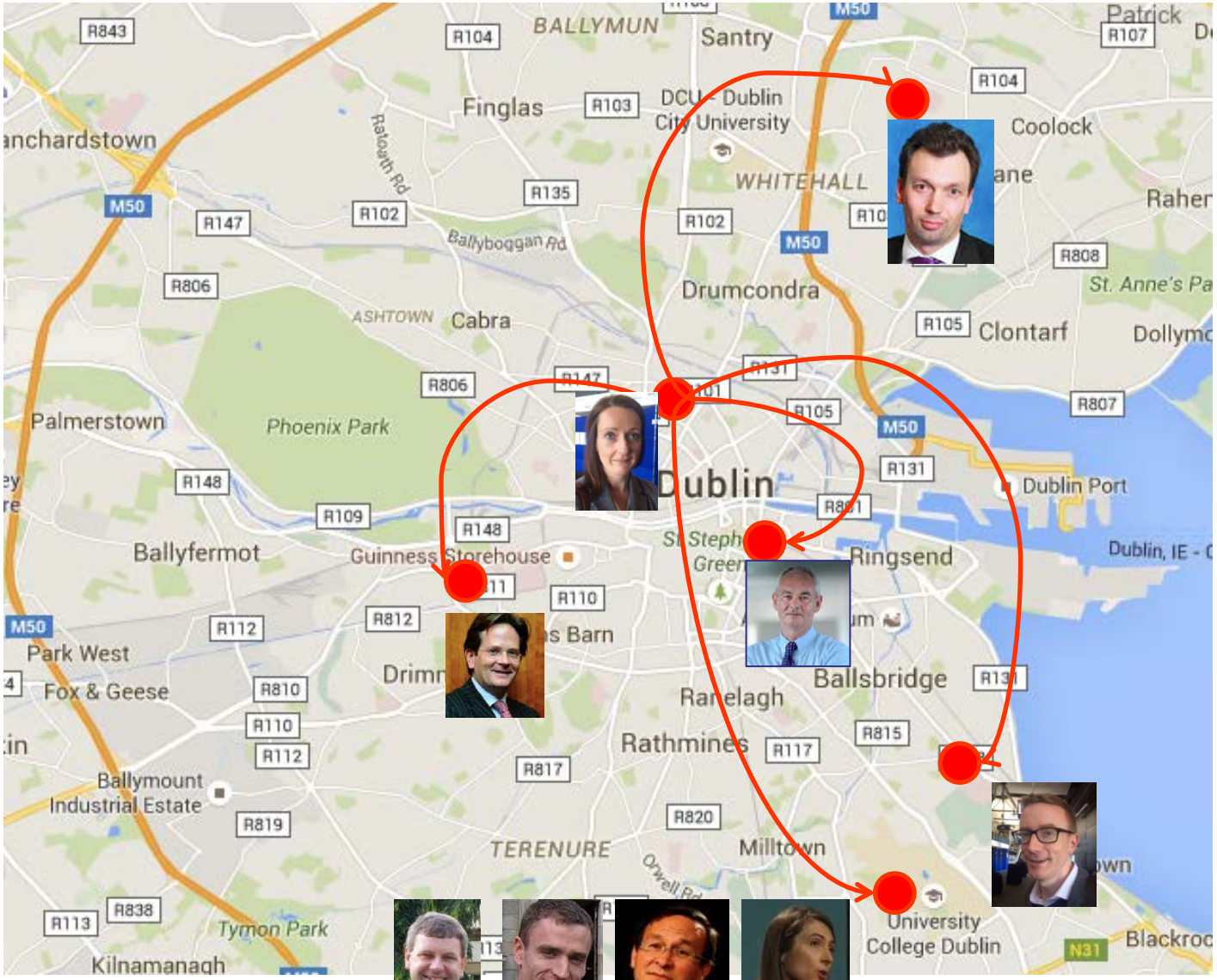
Project management







Building research - collaboration



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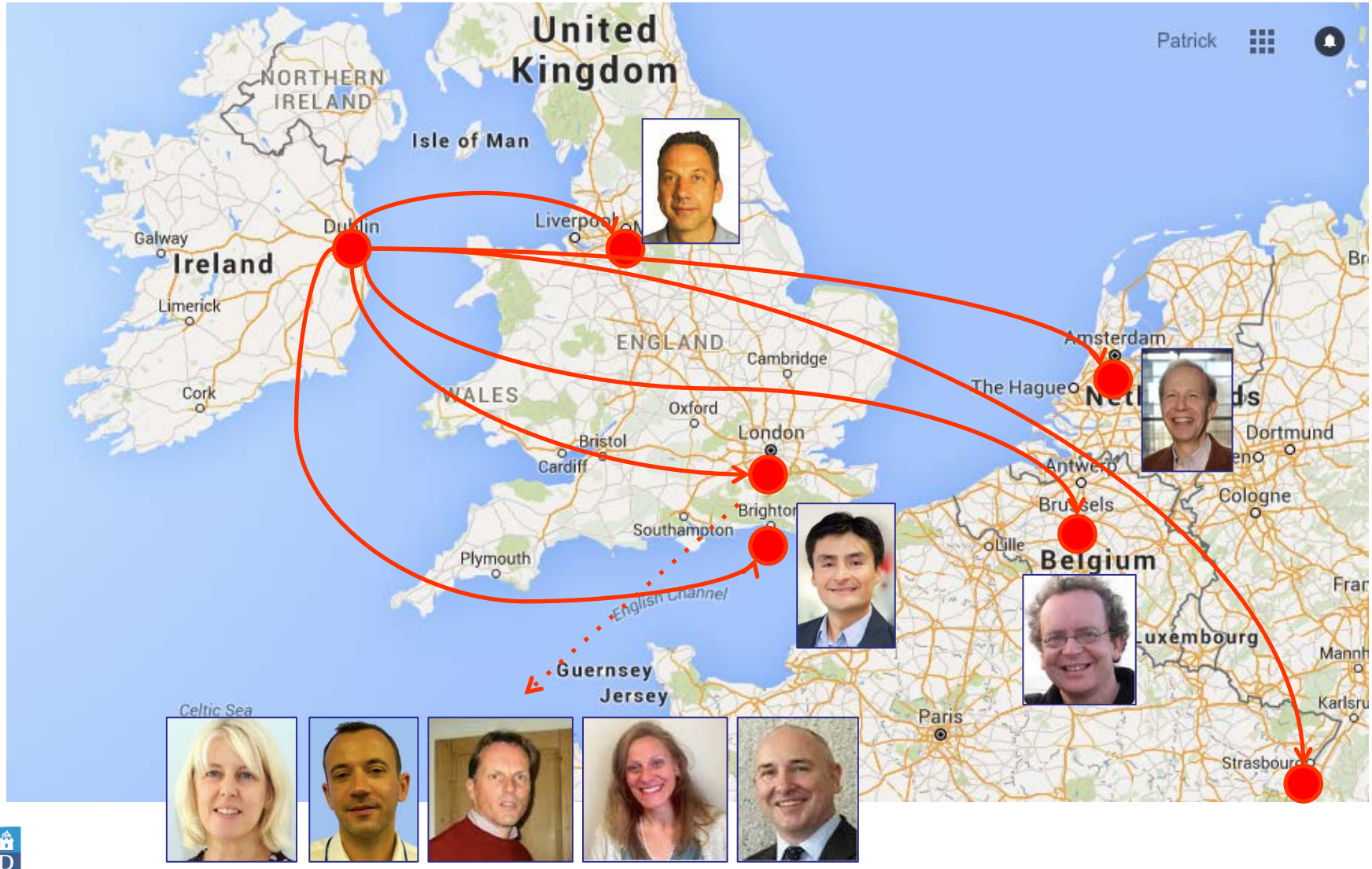
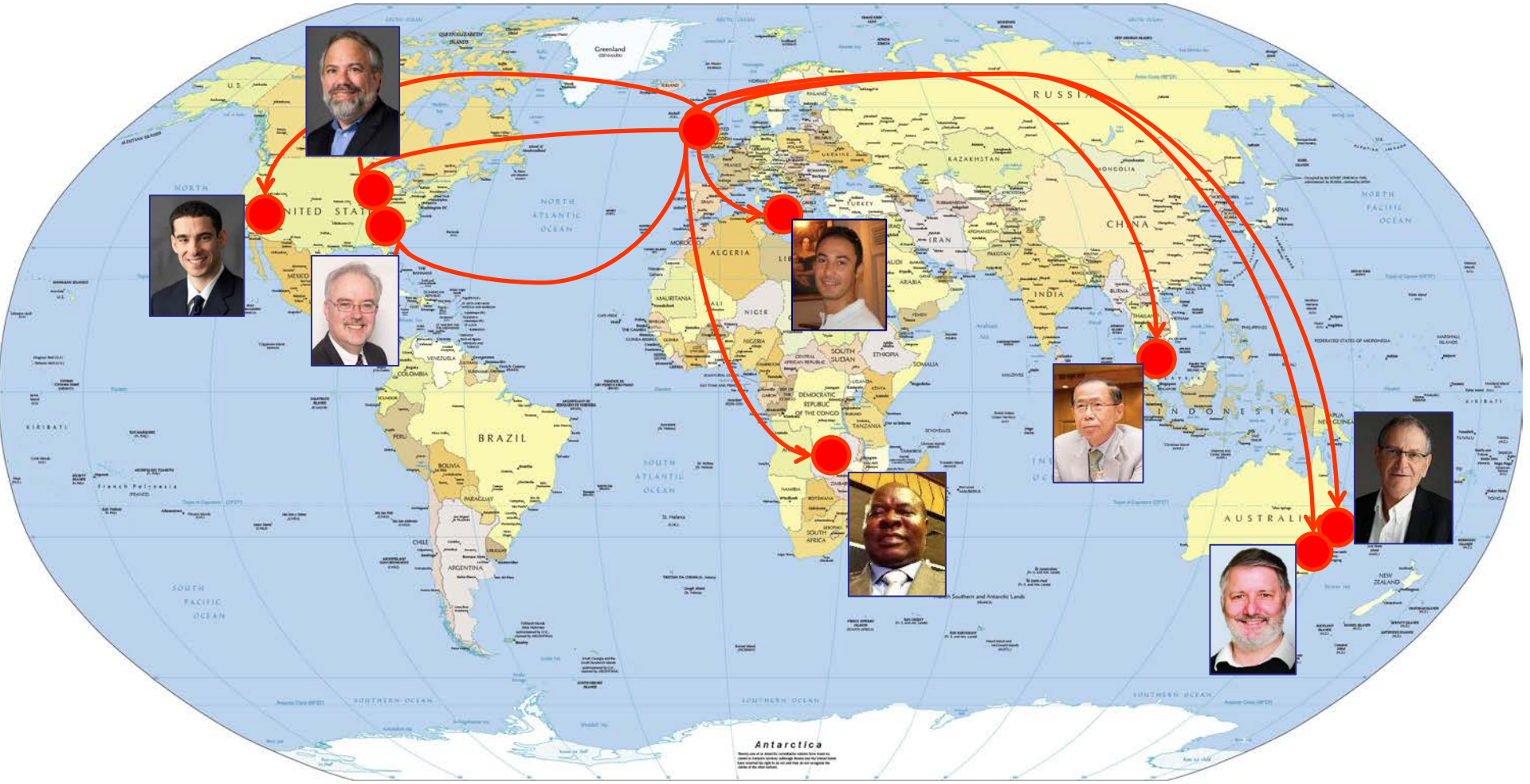


Building research - collaboration



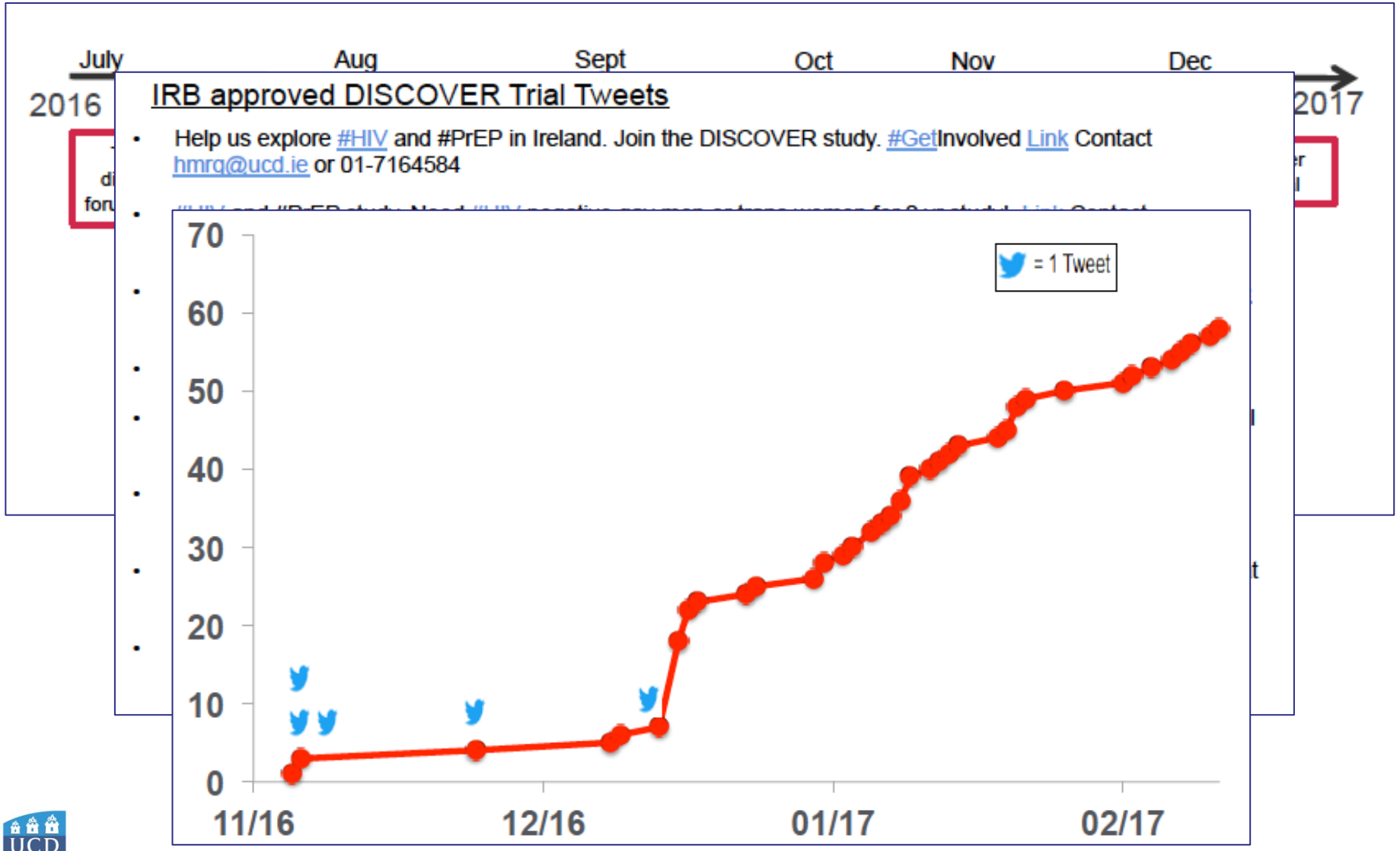
Building research

Building collaborations and growing expertise within the team enables more complex research

Patient & Public Involvement (PPI)

Dissemination and impact - social media!

Dissemination and impact - social media!



Implementation of research

- Challenging aspect of research
- Different kind of discipline
- Stakeholder involvement essential
- Create an '*environment for change*'
  - Hepatitis C……

Summary

Research is fun!

Surround yourself with like-minded people

Seek ways to collaborate

Try not to be too focused

Establish links with stakeholders – PPI

Never give up!

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