The British Society for Rheumatology’s Biologics Register

Mervyn Hogg
Clinical Project Manager, BSR
Topics

• Programme Objective
• Project Design
• Recruitment
• Governance
• Publications Process
• Events Attribution
• Plans
• Trends, Needs and Futures
Programme Objective

• Does anti-TNFα therapy in patients with rheumatoid arthritis (RA) increases the risk of malignancy, important co-morbidity and severe infection?

• How are these risks characterized?
  – any relationship to dosage or duration of therapy?
  – any specific disease characteristics that act synergistically to increase the risk?
  – do multiple biological agents act synergistically to increase the risk?

• Using normal clinical indicators, what are the risk/benefit ratios for adverse outcomes?
An Unique Research Collaboration

• A ground-breaking way to do post-license pharmacovigilance with:
  – leadership and direction managed by a professional medical society,
  – independent data management and ethics committee,
  – active interest and support from NICE,
  – funding from the pharmaceutical industry,
  – pan-UK participation by consultant rheumatologists supported by allied health professionals,
  – data management and analyses provided through the arc EU, who maintain academic independence,
  – ownership of the intellectual property generated by the register vested in the British Society for Rheumatology.
Project Design
Recruitment and Follow-up

- Consultant questionnaire: 5 YEARS
- Patient questionnaire & diary: 3 YEARS
- Office for National Statistics (ONS) flagging: LIFE LONG

Year 0 | Year 3 | Year 5
Anti-TNFα Patient Recruitment

• Patients drawn from all UK clinics and consultants.

• Registration of all patients receiving anti-TNFα treatments for rheumatoid arthritis mandated by NICE guidance.

• Finite target of 4000 patients per treatment; thereafter newly-treated patients not required to be registered.
DMARD Control Cohort Centres

29 Centres across the UK
Target 3900 patients
Recruitment and Cohort Entry Characteristics
## Patient Enrolment for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Company</th>
<th>Patient Target</th>
<th>RA Register Cohort</th>
<th>Enrolled per quarter in 2005-6</th>
<th>Patients Required</th>
<th>Enrolment Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>Abbott</td>
<td>4,000</td>
<td>2,627</td>
<td>212</td>
<td>1,373</td>
<td>Q2, 2008</td>
</tr>
<tr>
<td>anakinra (1)</td>
<td>Amgen</td>
<td>2,500</td>
<td>92</td>
<td>0</td>
<td>2,410</td>
<td>∞</td>
</tr>
<tr>
<td>etanercept</td>
<td>Wyeth</td>
<td>4,000</td>
<td>4,312</td>
<td>Closed 500 in 2004-5</td>
<td>0</td>
<td>Complete</td>
</tr>
<tr>
<td>infliximab (2)</td>
<td>Schering Plough</td>
<td>4,000</td>
<td>3,928</td>
<td>74</td>
<td>72</td>
<td>Q4, 2006</td>
</tr>
<tr>
<td>Total anti-TNFα excluding (1)</td>
<td>-</td>
<td>12,000</td>
<td>10,867</td>
<td>286</td>
<td>1,445</td>
<td>-</td>
</tr>
<tr>
<td>DMARD Controls</td>
<td>-</td>
<td>3,900</td>
<td>2,846</td>
<td>217</td>
<td>1,054</td>
<td>Q1, 2008</td>
</tr>
</tbody>
</table>

Data as of 30th September 2006
(2) Recruited includes 410 retrospective patients
## Baseline Characteristics - 1st March 2006

<table>
<thead>
<tr>
<th></th>
<th>Comparison cohort (n = 2309)</th>
<th>Anti-TNF cohort (n = 9339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, sd)</td>
<td>60 (12)</td>
<td>54 (12)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>72%</td>
<td>74%</td>
</tr>
<tr>
<td>Disease duration (median, IQR)</td>
<td>12 (6-19)</td>
<td>7 (1-15)</td>
</tr>
<tr>
<td>Steroid use (%)</td>
<td>22%</td>
<td>47%</td>
</tr>
<tr>
<td>DAS28 (mean, sd)</td>
<td>5.1 (1.4)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>HAQ (mean, sd)</td>
<td>1.5 (0.8)</td>
<td>2.1 (0.6)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>26%</td>
<td>22%</td>
</tr>
</tbody>
</table>
## Biologic Questionnaire Response Rates - 1\textsuperscript{st} March 2006

<table>
<thead>
<tr>
<th></th>
<th>No. patients</th>
<th>Hospital</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUP1</td>
<td>10,426</td>
<td>94%</td>
<td>76%</td>
</tr>
<tr>
<td>FUP2</td>
<td>9,261</td>
<td>90%</td>
<td>72%</td>
</tr>
<tr>
<td>FUP3</td>
<td>7,362</td>
<td>86%</td>
<td>72%</td>
</tr>
<tr>
<td>FUP4</td>
<td>5,348</td>
<td>85%</td>
<td>70%</td>
</tr>
</tbody>
</table>
Governance
Project Structure

Programme Management

Data, Ethics & Audit

Intellectual Property

Relationships Finance

Pharmaceutical Sponsors

Patients

Consultants & Nurses

NHS

National Institute for Health and Clinical Excellence

The University of Sheffield

BSR

Epidemiology Unit
Manchester University

Wyeth

Abbott Laboratories

AMGEN®

Schering-Plough

7th Dec 2006 BSR Biologics Register at NICE
Meetings

• BSR Steering Committee
  – Quarterly meetings to manage and direct the execution of the project

• BSR Executive
  – One Session per annum to consider overall strategy, direction and objectives for the Register

• BSR-arc EU monthly Telephone Conferences
  – address immediate operational topics

• BSR and Pharma meetings
  – Annual 1:1 meetings and a Joint meeting to consider overall business management of the register e.g. business plans, publications process and data access
Motivation

• Arc EU Data Management Team hold regular meetings with Control Centres
• Open Meetings for all participants held during the BSR Annual Conference
• Annual survey of consultants with a report of finding at the open meeting and subsequent publication
• BSR produces a Newsletter that reviews progress and provides news of all presentations and publications
• Broadening range of contributors and authors for future publications
Publications Process
Publications Process

- Protection of intellectual property and confidentiality of data
- Timescales for preparing and submitting Abstracts for conferences
- Review of presentations for meetings and ‘local’ conferences
- Review process within BSR
- Review Process by pharmaceutical companies.
- Maintaining the academic independence of authors
Issues in Relation to Publications

Prior to 2005

- Great suspicion about sharing any data or results between companies that were seen as impacting their commercial position.
- Reports from BSR were sent out with 'blanked-out' results so that each company could only see its products results and those for DMARDS.
- Timescales for review of any kind of publication including all abstracts, posters and papers was a minimum of 30 days.
New Publications Review Process

Trialed in 2005
To be incorporated into contracts.
Publications Review

• All materials for preview provided as late draft ‘Beta’ versions with all results and graphics open to view (i.e. no blanking out by product of results).

• Decisions in relation to content and any revision to papers will be the responsibility of the authors, irrespective of their affiliation.

• Independence and commercial distance respected at all stages: correspondents either from the Companies or BSR, confined solely to important questions and matters concerning fact and accuracy of interpretation.

• All communications flow through BSR office.
Timescales for Publications
Reviews

• Review time: 10 business days (i.e. 15 calendar days)
  • Abstracts for conference presentations
  • Posters, presentation slide sets and papers that are going to used at a medico-scientific conference (e.g. ACR, BSR, EULAR)

• Review time: 20 business days (i.e. 30 calendar days)
  • Papers that are to be submitted for full publication in a scientific or medical journal.
  • Posters, presentation slide sets and papers that are going to used at a medico-scientific conference (e.g. ACR, BSR, EULAR) for which there has been material change in the results or conclusions from those submitted in the abstract.

• No review
  • Presentations using previously published or conference-presented material have no review. e.g. RCP or regional meetings given by the arc EU Investigators, Steering committee or BSR staff. Companies, and vice-versa, the BSR will as far as is practicable be advised of such meetings and receive a copy of the slide pack.

• Request Delay
  • For specific action to protect IP a delay of 30 days may be requested – unused so far.
Event Attribution for a sequence of treatments

Under development: as an aid to understand appropriate data sharing
Treatment, Action, Events and Attribution

Event:
- $E_1$
- $E_2$
- $E_3$
- $E_4$

Duration of action for $T_1$ & $T_2$:
- $A_{11}$
- $A_{12}$
- $A_{13}$
- $A_{14}$
- $A_{21}$
- $A_{22}$
- $A_{23}$
- $A_{24}$

Treatment:
- $T_1$
- $T_2$

Time-months: 0, 3, 6, 9, 12, 15, 18, 21, 24

7th Dec 2006
BSR Biologics Register at NICE
### ‘Truth Table’ for Event Attribution

<table>
<thead>
<tr>
<th>Action</th>
<th>E₁</th>
<th>E₂</th>
<th>E₃</th>
<th>E₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short- A₁₁</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Same- A₁₂</td>
<td>T₁</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Long- A₁₃</td>
<td>T₁</td>
<td>T₁</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>V. Long-A₁₄</td>
<td>T₁</td>
<td>T₁</td>
<td>T₁</td>
<td>T₁</td>
</tr>
<tr>
<td>Short- A₂₁</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Same- A₂₂</td>
<td>N</td>
<td>N</td>
<td>T₂</td>
<td>N</td>
</tr>
<tr>
<td>Long- A₂₃</td>
<td>N</td>
<td>N</td>
<td>T₂</td>
<td>T₂</td>
</tr>
<tr>
<td>V. Long-A₂₄</td>
<td>N</td>
<td>N</td>
<td>T₂</td>
<td>T₂</td>
</tr>
</tbody>
</table>

Caveat and caution: few absolutes, in reality most attributions are a balance of probabilities!
Plans
**Plans, partners & contracts**

- Contracts and Finances complex
  - Substantial multi-million £ project.
  - New Business Plan for 2006-2013 put in place and agreed with funding pharmaceutical companies.
  - Revised Contracts that reflect maturity of the project in development
- A large programme for an organisation like BSR
  - more companies are interested in joining so it is set to get larger
  - Business plan and proposed contracts address principles of more potential funding partners
  - Companies with new products may be added as additional resources to the programme.
    - each company might have a distinct protocol with requirements tailored to their medicine.
BSR and NICE Appraisals: in progress

Multiple Technology Appraisals (MTA)
- Adalimumab, etanercept and infliximab for Ankylosing Spondylitis
- Adalimumab, etanercept and infliximab for Rheumatoid Arthritis
- Etanercept and infliximab for Juvenile Idiopathic Arthritis

Single Technology Appraisals (STA)
- Adalimumab for Psoriatic Arthritis
- Leflunomide for Psoriatic Arthritis
- Rituximab for Rheumatoid Arthritis
- Abatacept for Rheumatoid Arthritis
Trends, Needs and Future
Trends and Needs

• Trends
  – Expect earlier and more aggressive use of biologics agents
    • UK around 4000 new patients per annum on anti-TNFα agents, i.e. about 5%
    • Scandinavia 15% receive anti-TNFα agents.
    • USA ~ 40% receive anti-TNFα agents
  – More agents being licensed will increase overall rate of treatment response
  – Switching to maintain response will become common place

• Needs
  – Better diagnostic and efficacy measures that aid treatment chose
  – Flexibility in registration and tracking patients and treatment usage that evolve with a changing medical practice
  – Health economic models that inform and assist treatment planning at the per patient level
Future

• Stronger partnership between BSR, NICE and other Regulatory Agencies.
• Work with Medical Societies within Europe to encourage the use of pharmacovigilance registers to support and inform clinical practice.
• BSR’s aim is to make best use of the unique resource that is the Biologics Register
Acknowledgements

• Samantha Peters, Chief Executive, BSR
• Ian Griffiths (Past Chair) and David Isenberg (Chair) BSR Biologics Register
• Members of the BSR Biologics Register Committee
• Alan Silman, Deborah Symmons, Principal Investigators and the staff of the arc Epidemiology Unit, Manchester
• Financial Support of the Pharmaceutical Companies.
Contact

Mervyn Hogg
BSR Biologics Register Manager

British Society for Rheumatology
Bride House, 18-20, Bride Lane,
London, EC4Y 8EE
Email: mhogg@rheumatology.org.uk