European databases: different steps to build a research network database

EuroWilson:
the first prospective Europe-wide study of Wilson’s Disease
Wilson’s disease (WD) is ......

• A genetic condition (recessive)
• Causing
  – Liver disease
  – Neurological disease
  – (anaemia, and eye, joint, & kidney problems)
• Caused by copper not being excreted by the liver
• Treatable
364 cases in 328 families
Male = female
1. Purpose
2. Register or database?
3. Case definition
4. Database content
5. Terms and language
6. Data quality and cleaning
7. Clinician co-operation
8. Team working
9. Consent & governance
10. Research ethics committees
11. Data handling
12. Access to the data
13. Sustainability
1. Purpose

To assess the feasibility of clinical trials in Wilson’s

Mission creep

additional aims

RISK = loss of focus

- “Whilst we are about it” eg epidemiology
- Quality eg EMQN
- Unexpected findings vertical transmission
- “a pity to stop”
2. Register or database?

**EW** is a clinical database of patients defined as having Wilson’s disease.

A register requires that all patients with [X] are notified to it.

Attempts complete ascertainment, but achieves its objectives without it.

e.g. statutory, mandatory, treatment related
3. Case definition

Only Wilson’s disease, eg. excludes carriers with confusing tests other similar diseases

Includes atypical cases may suggest additional tests

EW database

Validation cttee actively engages
4. Database content

“Let’s include everything in case we need it later”

“We must not over-burden the data-entering clinicians”

EW database

Core mandatory + Detailed desired
A group of English-speaking doctors thought everybody knew the meaning of words like ....
6. Data quality & cleaning

- Data
- EW database
- Diagnosis check
- Email or phone dialogue with clinician

Are the data complete? consistent? credible?

More data

Follow-up?
7. Clinician co-operation

So, data entry by a clinician:
1. Carries no financial reward
2. Does not confer formal specialist status upon the centre
3. Relies on goodwill, friendship, and Hippocratic principles
4. Does lead to names on publications & education

Relative merits of this vs
1. Heavily funded industry-led databases
2. Statutory registers
8. Team working

Paediatrician
“I don’t know what happens after they get to 16”

Neurologist
“The liver?”

Adult hepatologist
“I can fix the liver, but please don’t ask me to do a neurological examination”

ophthalmologists
psychiatrists
rheumatologists
haematologists
“I had a case once”
9. Consent & governance

*Is my data safe?*

- see [www.eurowilson.org](http://www.eurowilson.org) for information & consent forms for adults, children, & parents

- We regard patient data as a **conditional gift**, so
  1. Ownership of data passes from donor to Consortium
  2. The conditions of the gift are explicit in the consent form eg confidentiality, security, use of data

- An Oversight Committee with patient representatives and ethics expertise ensures probity
Why does my doctor look at my handwriting?

Sometimes people with Wilson’s disease have too much copper in the brain. This can cause problems like tremor which is shaking of the hands, or sometimes difficulties in talking, writing or buttoning up a shirt. Medical treatment will get rid of the copper slowly and prevent or stop these symptoms.
10. Research ethics committees

- REC approval initially in Coordinator’s country (UK)
- MREC imposed stifling condition that each data-entering clinician had LREC approval; appealed
- REC requirements varied hugely in participating countries; usually accepted version of UK MREC forms
- Concerns about cross-boundary flow of data

Suggestion: A European REC approval system for rare disease registers, agreed by all MS, would reduce delays and inconsistencies and increase rigour.
11. Data handling

uses an anonymised web-based system with CPS card security for entry and secure systems for storage and back-up

• mutual ignorance
• & lack of esteem
• different languages

Unexpectedly hard work to achieve and maintain dialogue
12. Access to the data

1. The data is owned by the Consortium
2. Applications for use, whether academic or commercial, are made to the Consortium (may refer to Oversight)
3. Permission for use should not be unreasonably withheld
4. An executive summary for public use is a condition of the FP6 grant
5. Publication rules laid down at the beginning in a binding Consortium Agreement
13. Sustainability

Having achieved its immediate goals, could be “mothballed,” **BUT**

Important new answerable questions have arisen. It is a unique resource and exemplar.

**Suggestion**

Maintenance of RD databases:
1. Should not depend on ad hoc funding
2. If coordinated at EU level, could achieve economies of effort and scale
Number of cases from Jan 2005 – July 2008 per 1000m population

Ascertainment or true incidence?

(Turkey 329)
Initial treatment

Number

- Zinc + penicillamine
- Zinc + trientine
- Zinc sulfate
- Zinc acetate
- Trientine
- Transplanted
- Penicillamine
### Initial doses used
**mg/kg/day**

<table>
<thead>
<tr>
<th>drug</th>
<th>Mean dose</th>
<th>minimum</th>
<th>maximum</th>
<th>Recommended adult dose</th>
<th>Adult dose in mg/kg for 70 kg person</th>
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</thead>
<tbody>
<tr>
<td>Zinc sulfate</td>
<td>3.2</td>
<td>1.0</td>
<td>21.7</td>
<td>50 mg x3</td>
<td>2.4</td>
</tr>
<tr>
<td>Zinc acetate</td>
<td>2.6</td>
<td>1.7</td>
<td>4.6</td>
<td>50 mg x 3</td>
<td>2.4</td>
</tr>
<tr>
<td>trientine</td>
<td>19.6</td>
<td>3.3</td>
<td>23.1</td>
<td>1.2-1.4 g/day</td>
<td>17-34</td>
</tr>
<tr>
<td>penicillamine</td>
<td>16.7</td>
<td>0.6</td>
<td>34.5</td>
<td>1.5-2.0 g/day</td>
<td>21-29</td>
</tr>
</tbody>
</table>
Thanks to

• the patients
• FP6
• the EuroWilson Consortium, Oversight Committee,
  staff, and data-entering clinicians
• and, if you have been, to you for listening