Establishing registries: Potential biases in the cohort analysis

Zsolt Szakács
Pécs, Hungary
Selection bias/confounding

Is the sample representative to the entire population?

A

B

Properties of A = Properties of B

Representativeness

Are the study-arms equal in all properties except for the exposure?

A1

A2

Properties of A1 = Properties of A2

Confounding
Hypothesis: aspirin reduces CV deaths in the elderly

Design: two-arm prospective study (500-500 patients)

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>No aspirin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female ratio</td>
<td>1:1.01</td>
<td>1:1.04</td>
<td>P=NS</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>71±10 y</td>
<td>64±9 y</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>10-y CV death</td>
<td>12%</td>
<td>4%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>10-y bleeding</td>
<td>16%</td>
<td>11%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

The hypothesis should be rejected because aspirin increases CV deaths
Confounding

Aspirin → CV deaths

Age (Comorbidities)

Cause → Effect

Confounding factor
Errors in epidemiological studies

Valid?  Precise?

Bias

Imprecision
Sample size - small? large?

Bias

Imprecision

Systematic error

Random error

Sample size↑ Risk↓ Sample size↑ Risk↓
COMMON MISTAKE

1. Effects of interventions are tested.
2. Selection bias is not taken into account.
1. Ideal for prognostic questions.
2. Ideal for trends, surveillance.
Thank you for your attention!

www.tm-centre.org
Establishing registries: How to create a case report form?

Dalma Erdősi
02 October 2019, Pécs
To find answers to a clinical question – if other methods do not work.
Translational Medicine

taking discoveries for patients’ benefit

Statistical, IT, data managing, monitoring help is included

Registry

1. Development

2. Data collection

3. Data analysis
What is a registry good for?

- Prospective data collection -> ask a clinical question after
- Pre-trial in research
- Calculate sample size for a clinical trial
- Understanding the course of a disease
- To optimize a protocol for a clinical trial
- Collect 'nice to have' data
- Long-term data collection
- Answering epidemiological, cross-sectional and risk factors of diseases
The registry is not suitable for:

- Establishing cause-effect relationships
- Answering therapeutic questions
- Distungishing between interventions
What should I focus on when starting a registry?

• Design, structure

• Monitoring-supervise

• Follow-up

• Close cooperation with other fields’ experts
Case report form (CRF), common questions

- Research in our already existing database
- Main parts:

<table>
<thead>
<tr>
<th>1.</th>
<th>2.</th>
<th>3.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient data</td>
<td>Anamnesis</td>
<td>Status/Admission details</td>
</tr>
<tr>
<td>4. Symptoms/Complaints</td>
<td>5. Examinations (laboratory, imaging)</td>
<td>6. Therapy, interventions</td>
</tr>
<tr>
<td>7. Complications, adverse events</td>
<td>8. Epicrisis, outcome</td>
<td></td>
</tr>
</tbody>
</table>
Case report form (CRF), common questions

Smoking: yes / no
if yes: amount (cigarettes/day): 
For how many years? 
if not: Did you smoke earlier? yes / no
if yes: amount (pcs/occasion): 
For how many years? 
How long ago did you stop smoking? 

Alcohol consumption: yes / no
if yes: frequency: occasionally/monthly/weekly/daily
amount (g/day): 
since when? (years): 
Alcohol consumption in the last 2 weeks: 
if not: Did you drink alcohol earlier? yes / no
if yes: frequency: occasionally/monthly/weekly/daily
amount (g/occasion): 
For how many years? 
How long ago did you stop drinking alcohol?
Question and answer types

Clear notation

• Input data (i.e.: text, number, date-year-month-day)
• Dependency (if yes…, if no…)
• Relating questions
• Single or multiple choice
• Sections
• Modification
Question and answer types

Clear notation

No data is also important data

Less free text

Better database

Always start from the maximum amount of data

Categorical

Continuous
Thank you for your attention!
Establishing registries: Overview, final acceptance and translation

Zsolt Szakács
Pécs, Hungary
A difficult equilibrium: Collect more to have more potential of analyses or less to ensure better compliance?

Prioritise the data to at least 2 categories:

- Mandatory
- Optional
Process of the final approval of the registry plan within the TMC (after the inception and referral of the idea to the registry coordination team).

1. Approval by the registry coordinator (Vivien Vass)
2. Interdisciplinary review (IT, biostatistician, data management coordinator, strategic lead)
National and international review of the planned registry.

- National review
  - Courtesy
- International review
  - Choose the best

Involve the experts (external institutions) in the planning who will contribute to the database.
Translation. Don’t get lost in it!

- Always start in English
- Translate it to your own language afterwards
- Translate it to other languages when it is launched in a new country
Test your data collection strategy after ethical approval but before the IT development

• Your questionnaire and data collection may not be as feasible
• Change your data collection strategy and forms if necessary, before IT development starts
Risk of bias assessment

STOP COMMON MISTAKE

1. Too much unnecessary data
2. Missing important data
3. No external (national, international) or interdisciplinary review
Risk of bias assessment

TAKE HOME MESSAGE

1. Optimes and prioritise the amount of data to be collected
2. Get others view (external and interdisciplinary review)
Thank you for your attention!

www.tm-centre.org
Establishing a Registry: Ethical Approval

Dominika Tóth
CTM Patient Registry Course
2 October 2019, Pécs
Why Do We Need Ethical Approval?

- It is obligatory for the operation of the registry
  - So that the results of researches can be proven by law
  - So that the interest of patients are protected
Process of Ethical Approvals: Overview

Patient Registry → Documentations → Submitting to relevant authorities → Ethical Licence

Modifications, if needed
Documentations: How Can The CTM Help You?

- Sample documents
- Checklist
- Documents involving the University of Pécs – provided
- BIOBANK operating licences for the University of Pécs and the University of Szeged – available
- Submission to the relevant authority
Ellenőrző lista

Kutatás címe: 
Témavezető neve: 
Támogató/sponsor: 
Témavezető kutatóhelye: 
Multicentrikus vizsgálat esetén a részt vevő kutatóhelyek száma: 
Tervezett kutatás kezdete: 

Dokumentumok: 

1. Magyar nyelvű összefoglaló 
2. Magyar nyelvű kutatási terv 
3. A pályázattal megtegedt tartalmú CD 
4. Témavezető szakmai önélétrajza, publikációs listája* 
5. Multicentrikus vizsgálatnál az összes kutatóhely vezető kutatójának az önélétrajza, publikációs listája* 
6. Témavezető orvosi diplomával rendelkezik-e? 
7. Beteg illetve kutatási bevont személy táplálkozása 
8. Beteg illetve kutatási bevont személy beleegyező nyújtások  
9. Betegbébozás része a kutatásnak? 
10. Amennyiben a betegbébozás része a kutatásnak, a toborzás módja 
11. Plazebo csoportra szükség van-e? 

Table: | Dokumentumok | igen | nem | szükséges |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>3. A pályázattal megtegedt tartalmú CD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Témavezető szakmai önélétrajza, publikációs listája*</td>
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<td></td>
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<tr>
<td>5. Multicentrikus vizsgálatnál az összes kutatóhely vezető kutatójának az önélétrajza, publikációs listája*</td>
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<td></td>
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<tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10. Amennyiben a betegbébozás része a kutatásnak, a toborzás módja</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11. Plazebo csoportra szükség van-e?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rövid kutatási terv magyarul (absztrakt, mag, 1 oldal): 

Részletes vizsgálati terv, amely tartalmazza az alábbi felsorolt több pontot: 

A vizsgálat célja
Documentations: What We Need Registry Leaders To Do

- Detailed protocol regarding inclusion/exclusion criteria and the collecting of biological samples
- Documents needed when joining research projects:
  - Letter of Intent of Joining Research Project
  - Admission Letter
  - Letter of Intent
  - Financial Statement
  - Statement of Data Protection
  - Helsinki Statement
- Case Report Forms
  - In Hungarian
Documentations:
What We Need Registry Leaders To Do

- Patient Leaflets and Informed Consent
  - *In case of genetic research: another one is required*
- CVs and List of Publications
- Insurance Documents
Submitting To Relevant Authorities

- **Scientific and Research Committee (TUKEB)**
  - Application for Ethical Approval
  - Check-list of Ethical Application

- **Ministry of Human Resources (Deputy State Secretariat of Chief Medical Officer’s Affairs - OTH)**
  - In case of Biomedical Research Involving Human Subjects
  - Scientific and Research Committee sought out as relevant department

- **Regional Medical Research Council (RIKEB)**
  - Retrospective Data Collection
  - Only local
  - Ethical Committee
Take-Home Message

• Following the process of ethical approvals is key
• The CTM is always there to help
Establishing registries: IT development

Ferdinánd Henth
IT Team

Digital Ltd. Szeged

• System developer team with 6 people

• Their tasks:
  • ECDMS system development
  • Development of core modules
  • Release updates

Péter Nagy

• Developer of the previous (Drupal) system

Translational medicine IT Pécs

• Team of 2 people

• Our tasks:
  • Registry and study form developments
  • Validation development in the future
  • Registry publication to the test database
  • Keep in touch with the medical team
New registry development

Discussions
- Review of the completed documentation
- Paper-based test of the registry documentation

Development
- Searching for common fields
- Start development

Testing
- Test surface verification: IT team, administrative team, professional team

Validations
- Publication and testing the test surface again

Finalization
- Finalize the registry

Resolutions
- Resolution of the problems

Questions about the development
Answers for the questions

Publication and testing the test surface again
Create validations
• Aspects of testing:
  • Labels and dependencies are all correct
  • All translations are available
  • Calculations are all correct
  • Unit Exchange
  • Validations are all correct
  • Are all the questions included in the form?

• Phases of testing:
  • Phase 1: testing the structure of the forms
  • Phase 2: Testing after the validation, testing the calculated fields

• Method of testing:
  • Filled with test data to answer everything and with real data before and after validation
  • **Recommended number of upload test**: 5 - 10 case which includes extreme cases (all problems), 5-10 case with real patient data
Reasons behind necessary steps

Importance of deadline:
• real-time feedback after release the test version. E.G.: do not take several weeks for feedback with 1-2 change requests. This will speed up the process.

Reason for changes every six months:
• Common fields make it difficult to modify retrospectively in a released interface because it can affect many registers and may require data management, such as date fields or unit changes
Validations - Why is it important to use it?

Eliminate dimensions and errors without human intervention.

Data quality improvement → High quality data

Other Examples:

• One date must be after another (birth < procedure)
Validations

Other Examples:

- If idiopathic is the answer, it can't be the other

<table>
<thead>
<tr>
<th>Condition</th>
<th>Options</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>yes, no, &lt;no value&gt;</td>
<td>no data</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>yes, no, &lt;no value&gt;</td>
<td>If etiological factor was identified, please answer “no” to “Idiopathic”.</td>
</tr>
<tr>
<td>Congenital anatomical malformation</td>
<td>yes, no, &lt;no value&gt;</td>
<td>no data</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>yes, no, &lt;no value&gt;</td>
<td>If etiological factor was identified, please answer “no” to “Idiopathic”.</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy</td>
<td>yes, no, &lt;no value&gt;</td>
<td>no data</td>
</tr>
<tr>
<td>Genetic</td>
<td>yes, no, &lt;no value&gt;</td>
<td>no data</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>yes, no, &lt;no value&gt;</td>
<td>If etiological factor was identified, please answer “no” to “Idiopathic”.</td>
</tr>
<tr>
<td>Other</td>
<td>yes, no, &lt;no value&gt;</td>
<td>no data</td>
</tr>
</tbody>
</table>
Typical traps

Clear notation of input data (number, text, fraction, etc.)

For automatic calculations, enter the formula

Specify shift numbers for multiple units

The laboratory value should always be a unit, if available.

For date fields, what is required and what is optional (e.g.: only year is required)

Make clear in the options listed that you can only select one or more at a time

Modify requests, formulate clear and precise requests: on which tab (section), which question to replace.

Often there are options without questions. Everything should have a question, a description of what they are answering.
Thank you for your attention!
Operating a Registry: Patient Involvement and Data Quality Control

Péter J. Hegyi
CTM Patient Registry Course
2 October 2019, Pécs
Engage your patient
Patient information leaflet and informed consent

Age groups

• 7-10 years
• 10-14 years
• 14-18 years
• above 18 years
Decision making capacity

- confused or demented patients

Illiteracy

- witness
Engage your patient

Show and explain!
• decision aids
• graphical tools
• interactive media
Engage your patient

Benefits
• Improves patient care
• Saves lives
• Saves money

Disadvantages
• Administrative tasks
Biobank

- separate information leaflet and informed consent
- no additional intervention
Collecting data

Patient involvement

Patient questionnaire

Collecting data

Data upload
Quality assurance

- 1. Data upload by the administrator
- 2. Local medical supervision and approval
- 3. Approval by leading clinical research administrator
- 4. Approval and verification by Principal Investigator
4. check mark

Common mistakes

- Severity
- Complications
- Imaging examination findings: interpretations
- Medication dose, unit
Take-home message

• PATIENT INVOLVEMENT: patient-centered clear information

• COLLECTING DATA:

• QUALITY CONTROL
Thanks for your attention!
Operating a registry: 
Data Collection and Quality

Emőke Miklós
Pécs, Hungary
Tasks of Datamanagement group

- Collecting data: inclusion and questioning of patients, application of data resources (MedSol, laboratory results etc.)
- Data is recorded on the interface
- Verified
- Corrected
- Case reports form
- Protocols
- Collecting, storing, transporting of biological samples
The Tasks of Clinical Research Administrators (CRA):

Clinical trial datamanagers vs. clinical research administrator (CRA)

- Meta-analyses
- Registries
- Clinical trials
- Retrospective data collection
Data quality – Education of CRA

- CRA meetings (if needed)
- CRA vocational training (Type B) – start in December 2019
- Yearly CRA Training(in Vecsés)
- GCP- Good Clinical Practice
• Personal contact with the external centres discover, solve problems
• One trip/month (Székesfehérvár, Szeged, Debrecen). Expected extensions (Budapest, Békéscsaba, etc.)
• Weekly monitoring on every Friday (Skype/phone)
Quality control - Approval system (4 checkmarks)

Common errors:

- Long time between the collection and the upload of data
- 2., 4. checmarks are missing or late
Take home message

• Professional team:
good quality of training → good quality of data

• Good protocol and user’s guide

• The sooner the data is recorded in the data base the smaller is the risk of data loss and damage
Thank you for your attention!

Miklós Emőke
emimiklos@gmail.com

www.tm-centre.org
PATIENT CLUBS

Anna Vágási

Registry Course
Pécs, 2019.10.02.
AIMS AND IMPORTANCE

- support
- compliance improvement
- education
- interest representation
- prevention
- relations
THE BEGINNING

Registry starts out

Contact

Patient Club created
PATIENT INVOLVEMENT

- in the hospital the clinical research administrators give our brochures and the application forms to the patients, and inform them about the patient clubs.

- patients can also find out more about the clubs online and they can apply at our website too.
HOW DO WE SHARE INFORMATION?

Offline

Online
HOW DO WE SHARE INFORMATION?
HOW DO WE SHARE INFORMATION?
Why is creating a patient club recommended for everyone?
Together, we are louder!
THANK YOU FOR YOUR ATTENTION!
Establishing a Registry:
Common Problems and How to Solve Them
Please turn on your laptops
Connect to WiFi

WiFi:  
Password:

And go to this link:  
www.regcourse.ecdms.org
When adding new patients, please use your own:

- Social Security Number
- Name
- Birthday (using your own is optional, but leaving the field blank isn’t)

*Everything has to be filled out*
New | RGC-A

Institute: Pécs Kórház és Rendszámzélet (14)
Patient: -
Physician: <no value>

The operations work on form level.

Save Draft  Finalize  Cancel
Add New Patient

Insurance number:

Gender:
- Male
- Female

Date of birth:

Save  Cancel
New | RGC-A

Institute: Pécs Kórház és Rendelőintézet (14)

Patient: 

Physician: 

- <no value>
- Azulikos Zuzsanna

The operations work on form level

Save Draft  Finalize  Cancel
<table>
<thead>
<tr>
<th>Form id</th>
<th>State</th>
<th>Approval state</th>
<th>Physician</th>
<th>Form date</th>
<th>Recording date</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2507/A180007010</td>
<td></td>
<td></td>
<td>Prof. Dr. Medeiros</td>
<td>5/7/2018 12:00 PM</td>
<td>9/4/2018 11:37 AM</td>
</tr>
<tr>
<td>C2075/B10202113</td>
<td></td>
<td></td>
<td>Dr. Bajor Judit</td>
<td>2/21/2018 02:00 PM</td>
<td>2/19/2018 09:48 AM</td>
</tr>
<tr>
<td>C005/A0062012</td>
<td>update correction</td>
<td></td>
<td>Dr. Bajor Judit</td>
<td>6/26/2018 02:00 PM</td>
<td>1/22/2019 10:56 AM</td>
</tr>
</tbody>
</table>
Family history

Family disorders: Yes

If yes, please specify:

Tumorous disease in family history: Yes

If yes, please specify:

Tumorous disease in family history:

- **Type:** Breast cancer
- **Relationship to patient:** maternal grandmother

Other disease in family history: Yes

If yes, please specify:

List of known diseases:

- **Known disease:** Hypertonia
- **Relationship to patient:**
- **Known disease:** Diabetes mellitus
### Family History

<table>
<thead>
<tr>
<th>Family disorder?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumorous disease in family history?</td>
<td>Yes</td>
</tr>
<tr>
<td>Tumorous disease in family history</td>
<td><strong>Type:</strong> Breast cancer</td>
</tr>
<tr>
<td>Relationship to patient:</td>
<td><strong>Mother:</strong></td>
</tr>
<tr>
<td>Other disease in family history?</td>
<td>Yes</td>
</tr>
<tr>
<td>List of known diseases</td>
<td><strong>Known disease:</strong> Hypertonia</td>
</tr>
<tr>
<td>Relationship to patient:</td>
<td><strong>Mother:</strong></td>
</tr>
<tr>
<td>Known disease:</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Relationship to patient:</td>
<td><strong>Mother:</strong></td>
</tr>
</tbody>
</table>
2. Details of Medical History

Problem: Diet – cannot chose more than one option

Solution: Chose option „Other“
When creating the registry, the types of answers should be taken into consideration, and multiple-choice options should be selected accordingly.
4. Symptoms/Complaints
Abdominal pain – diffuse/localised

Prevention

*Forms should be filled out with the outmost precision by trained administrators*
4. Symptoms/Complaints

Vomiting – *can only chose from the pre-established options*

**Prevention**

*When creating the registry, the „Other” option should be available*
Problem
No clear distinction between given answers

An option has been marked and scratched out – there is no date or signature of correction

Solution
If the correct answer cannot be distinguished based on logic, clarification is needed from the responsible administrator
Problem

5. Examination
Lab results – changing units is sometimes forgotten

Solution

Forms should be filled out with the outmost precision by trained administrators