

Research question and Research design in Clinical research

Ayat Ahmadi, Epidemiologist

Assistant professor in Tehran University of Medical Sciences

Clinical research

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?
- c. What is an 'answerable' question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?
- c. What is an ‘answerable’ question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

Sources and examples of questions.

The focus and nature of these questions varies according to the **perspective of the stakeholder**. Patients focus on issues of most relevance to their specific situation, such as relief of symptoms; the clinician or researcher considers broader issues, for example choosing from a range of intervention options; colleagues and funders seek justification of interventions and funding allocation, respectively.

Source	Example
Patients	Can I return to work after my brain injury rehabilitation? How long will this pain last?
Own clinical/research experience	What is the best way to prevent and manage spasticity in Traumatic Brain Injury (TBI) patients? What is the impact of Spinal Cord Injury (SCI) on patients and their families?
Colleagues	Why did you do a CT instead of an MRI for this TBI patient?
Funders	Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?

Sources and examples of questions.

The focus and nature of these questions varies according to the **perspective of the stakeholder**. Patients focus on issues of most relevance to their specific situation, such as relief of symptoms; the clinician or researcher considers broader issues, for example choosing from a range of intervention options; colleagues and funders seek justification of interventions and funding allocation, respectively.

Source	Example
Patients	Can I return to work after my brain injury rehabilitation? How long will this pain last?
Own clinical/research experience	What is the best way to prevent and manage spasticity in Traumatic Brain Injury (TBI) patients? What is the impact of Spinal Cord Injury (SCI) on patients and their families?
Colleagues	Why did you do a CT instead of an MRI for this TBI patient?
Funders	Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?

Sources and examples of questions.

The focus and nature of these questions varies according to the **perspective of the stakeholder**. Patients focus on issues of most relevance to their specific situation, such as relief of symptoms; the clinician or researcher considers broader issues, for example choosing from a range of intervention options; colleagues and funders seek justification of interventions and funding allocation, respectively.

Source	Example
Patients	Can I return to work after my brain injury rehabilitation? How long will this pain last?
Own clinical/research experience	What is the best way to prevent and manage spasticity in Traumatic Brain Injury (TBI) patients? What is the impact of Spinal Cord Injury (SCI) on patients and their families?
Colleagues	Why did you do a CT instead of an MRI for this TBI patient?
Funders	Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?

Sources and examples of questions.

The focus and nature of these questions varies according to the **perspective of the stakeholder**. Patients focus on issues of most relevance to their specific situation, such as relief of symptoms; the clinician or researcher considers broader issues, for example choosing from a range of intervention options; colleagues and funders seek justification of interventions and funding allocation, respectively.

Source	Example
Patients	Can I return to work after my brain injury rehabilitation? How long will this pain last?
Own clinical/research experience	What is the best way to prevent and manage spasticity in Traumatic Brain Injury (TBI) patients? What is the impact of Spinal Cord Injury (SCI) on patients and their families?
Colleagues	Why did you do a CT instead of an MRI for this TBI patient?
Funders	Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?

Sources and examples of questions.

The focus and nature of these questions varies according to the **perspective of the stakeholder**. Patients focus on issues of most relevance to their specific situation, such as relief of symptoms; the clinician or researcher considers broader issues, for example choosing from a range of intervention options; colleagues and funders seek justification of interventions and funding allocation, respectively.

Source	Example
Patients	Can I return to work after my brain injury rehabilitation? How long will this pain last?
Own clinical/research experience	What is the best way to prevent and manage spasticity in Traumatic Brain Injury (TBI) patients? What is the impact of Spinal Cord Injury (SCI) on patients and their families?
Colleagues	Why did you do a CT instead of an MRI for this TBI patient?
Policy/ Funders	Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?**
- c. What is an ‘answerable’ question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

Which questions should be pursued?

This task is influenced by a range of factors including **time** and **resource** limitations, clinical **urgency**, organizational or local **research agendas** and **funding** sources.

- **Importance** of question to the patient's biologic, psychologic or sociologic well-being.
- **Relevance** of question to you/your learners' knowledge needs.
- **Feasibility** of answering question in the time available.
- Level of your/your learner's/your patient's **interest** in question.
- Likelihood of question **recurring** in your practice.

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?
- c. What is an ‘answerable’ question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

What is an ‘answerable’ question?

What is an ‘answerable’ question?

- An ‘answerable’ question in research terms is one which seeks **specific** knowledge, is framed to **facilitate literature searching** and therefore, follows a semi-standardised structure.

‘Answerable’ clinical research questions have four essential ‘PICO’ components:

- P: Patient and/or problem;
- I: Intervention (or exposure, diagnostic test, prognostic factor, etc.)
- C: Comparison Intervention (if relevant);
- O: Outcome.

“In [Population], what is the effect of [Intervention] on [Outcome], compared with [Comparison Intervention]?”

What is an ‘answerable’ question?

Original question	Answerable clinical research question (PICO elements in italics)
What is the best way to prevent and manage spasticity in TBI patients?	In patients with severe TBI , what is the effect of casting on spasticity, compared with pharmacological management?
Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?	In patients following SCI rehabilitation, what is the effect of community-based physiotherapy on functional status , compared with standard care ?
Why did you do a CT instead of an MRI for this TBI patient?	In patients with suspected TBI , what is the diagnostic value of CT , compared with MRI ?

What is an ‘answerable’ question?

Original question	Answerable clinical research question (PICO elements in italics)
What is the best way to prevent and manage spasticity in TBI patients?	In patients with severe TBI , what is the effect of casting on spasticity, compared with pharmacological management?
Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?	In patients following SCI rehabilitation, what is the effect of community-based physiotherapy on functional status , compared with standard care ?
Why did you do a CT instead of an MRI for this TBI patient?	In patients with suspected TBI , what is the diagnostic value of CT , compared with MRI ?

What is an ‘answerable’ question?

Original question	Answerable clinical research question (PICO elements in italics)
What is the best way to prevent and manage spasticity in TBI patients?	In patients with severe TBI , what is the effect of casting on spasticity, compared with pharmacological management?
Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?	In patients following SCI rehabilitation, what is the effect of community-based physiotherapy on functional status , compared with standard care ?
Why did you do a CT instead of an MRI for this TBI patient?	In patients with suspected TBI , what is the diagnostic value of CT , compared with MRI ?

What is an ‘answerable’ question?

Original question	Answerable clinical research question (PICO elements in italics)
What is the best way to prevent and manage spasticity in TBI patients?	In patients with severe TBI , what is the effect of casting on spasticity, compared with pharmacological management?
Why should we fund physiotherapy for patients following discharge from SCI rehabilitation?	In patients following SCI rehabilitation, what is the effect of community-based physiotherapy on functional status , compared with standard care ?
Why did you do a CT instead of an MRI for this TBI patient?	In patients with suspected TBI , what is the diagnostic value of CT , compared with MRI ?

What is an ‘answerable’ question?

There are some cases in which departure from the ‘generic’ PICO format:

- What *prognostic factors* influence *return to work* in *patients following TBI rehabilitation*?”
- “What is the *impact* of *SCI* on *patients and their families*?”

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?
- c. What is an ‘answerable’ question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?
- c. What is an ‘answerable’ question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

What is the question about?

‘PICO’ principles facilitates the important process of categorising the question according to its **central clinical issue**.

Therapeutic interventions are only one of a number of clinical issues that can be addressed by clinical research questions. There are many other categories including aetiology, prevention and differential diagnosis.

This process of categorisation is an important precursor to considerations of study design.

What is the question about?

Clinical research question	Category
In patients with severe TBI, what is the effect of casting on spasticity, compared with pharmacological management?	Therapy: selecting treatments that are effective and worthwhile
In patients with suspected TBI, what is the diagnostic value of CT, compared with MRI?	Diagnostic tests: selecting diagnostic tests with acceptable precision, safety, expense, etc.
What prognostic factors influence return to work in patients following TBI rehabilitation?	Prognosis: estimating likely clinical course and anticipating complications
What is the impact of SCI on patients and their families?	Experience and meaning: empathy and understanding of patient situations

What is the question about?

Clinical research question	Category
In patients with severe TBI, what is the effect of casting on spasticity , compared with pharmacological management?	Therapy: selecting treatments that are effective and worthwhile
In patients with suspected TBI, what is the diagnostic value of CT, compared with MRI?	Diagnostic tests: selecting diagnostic tests with acceptable precision, safety, expense, etc.
What prognostic factors influence return to work in patients following TBI rehabilitation?	Prognosis: estimating likely clinical course and anticipating complications
What is the impact of SCI on patients and their families?	Experience and meaning: empathy and understanding of patient situations

What is the question about?

Clinical research question	Category
In patients with severe TBI, what is the effect of casting on spasticity, compared with pharmacological management?	Therapy: selecting treatments that are effective and worthwhile
In patients with suspected TBI, what is the diagnostic value of CT, compared with MRI?	Diagnostic tests: selecting diagnostic tests with acceptable precision, safety, expense, etc.
What prognostic factors influence return to work in patients following TBI rehabilitation?	Prognosis: estimating likely clinical course and anticipating complications
What is the impact of SCI on patients and their families?	Experience and meaning: empathy and understanding of patient situations

What is the question about?

Clinical research question	Category
In patients with severe TBI, what is the effect of casting on spasticity, compared with pharmacological management?	Therapy: selecting treatments that are effective and worthwhile
In patients with suspected TBI, what is the diagnostic value of CT, compared with MRI?	Diagnostic tests: selecting diagnostic tests with acceptable precision, safety, expense, etc.
What prognostic factors influence return to work in patients following TBI rehabilitation?	Prognosis: estimating likely clinical course and anticipating complications
What is the impact of SCI on patients and their families?	Experience and meaning: empathy and understanding of patient situations

What is the question about?

Clinical research question	Category
In patients with severe TBI, what is the effect of casting on spasticity, compared with pharmacological management?	Therapy: selecting treatments that are effective and worthwhile
In patients with suspected TBI, what is the diagnostic value of CT, compared with MRI?	Diagnostic tests: selecting diagnostic tests with acceptable precision, safety, expense, etc.
What prognostic factors influence return to work in patients following TBI rehabilitation?	Prognosis: estimating likely clinical course and anticipating complications
What is the impact of SCI on patients and their families?	Experience and meaning: empathy and understanding of patient situations

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?
- c. What is an ‘answerable’ question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

Has the question been answered?

Once the key elements of the question have been specified and the broad question category identified, it is important to identify **how this or similar questions have been addressed by existing published research.**

Pub med	clinicaltrial.gov	web of sciences (ISI)	Cochrane collaboration(CDSR)
Embase	irct.ir	scopus	ERIC

Has the question been answered?

- Existing literature may focus on specific subgroups of *population* ,shows definition of the *population* might be reconsidered .
- Outcomes other than *outcome* may be more widely reported in the literature,prompting consideration of whether function is the most appropriate *outcome*;
- Particular study designs such as Randomised Controlled Trials (RCTs) may not be represented in relevant literature, raising questions of *feasibility* or *ethical* limitations to using such designs;
- There may be a large body of literature addressing this question but no systematic review,in which case a *systematic review* may be more useful than another primary study.

Has the question been answered?

- Many clinicians and researchers, particularly those not engaged in evidence-based medicine or systematic reviewing, baulk at the notion of spending their limited time performing an in-depth literature search at the question development stage. However, an investment of time at this point in the research process more than offsets the potential time and resources wasted in pursuing an inappropriate question, or one that has been comprehensively addressed already.

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?
- c. What is an ‘answerable’ question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

What research approach is appropriate?

quantitative and qualitative

Where research questions pertain to subjective phenomena such as feelings, attitudes and emotional responses, a qualitative research paradigm should be used. Qualitative research emphasises in-depth **exploration** and **description**, rather than numerical measurement, of variables. This results in a rich and **deep understanding** of the topic under study.

What research approach is appropriate?

Clinical research question	Data	Approach	Design example	Analysis example
In patients following SCI rehabilitation, what is the effect of community-based physiotherapy on functional status [Functional Independence Measure; FIM score] compared with standard care?	Numerical	Quantitative	RCT	Statistical
What is the impact [emotional responses, attitudes] of SCI on patients and their families?	Non-numerical	Qualitative	Focus group	Qualitative content analysis

Asking good questions:

- a. Sources and examples of questions.
- b. Which questions should be pursued?
- c. What is an ‘answerable’ question?

Choosing the right study design:

- a. What is the question about?
- b. Has the question been answered?
- c. What research approach is appropriate?
- d. What study design is appropriate?

What study design is appropriate?

Nature of the question

Clinical research question	Category
In patients with severe TBI, what is the effect of casting on spasticity, compared with pharmacological management?	Therapy: selecting treatments that are effective and worthwhile
In patients with suspected TBI, what is the diagnostic value of CT, compared with MRI?	Diagnostic tests: selecting diagnostic tests with acceptable precision, safety, expense, etc.
What prognostic factors influence return to work in patients following TBI rehabilitation?	Prognosis: estimating likely clinical course and anticipating complications
What is the impact of SCI on patients and their families?	Experience and meaning: empathy and understanding of patient situations

What study design is appropriate?

Sterengh of evidence

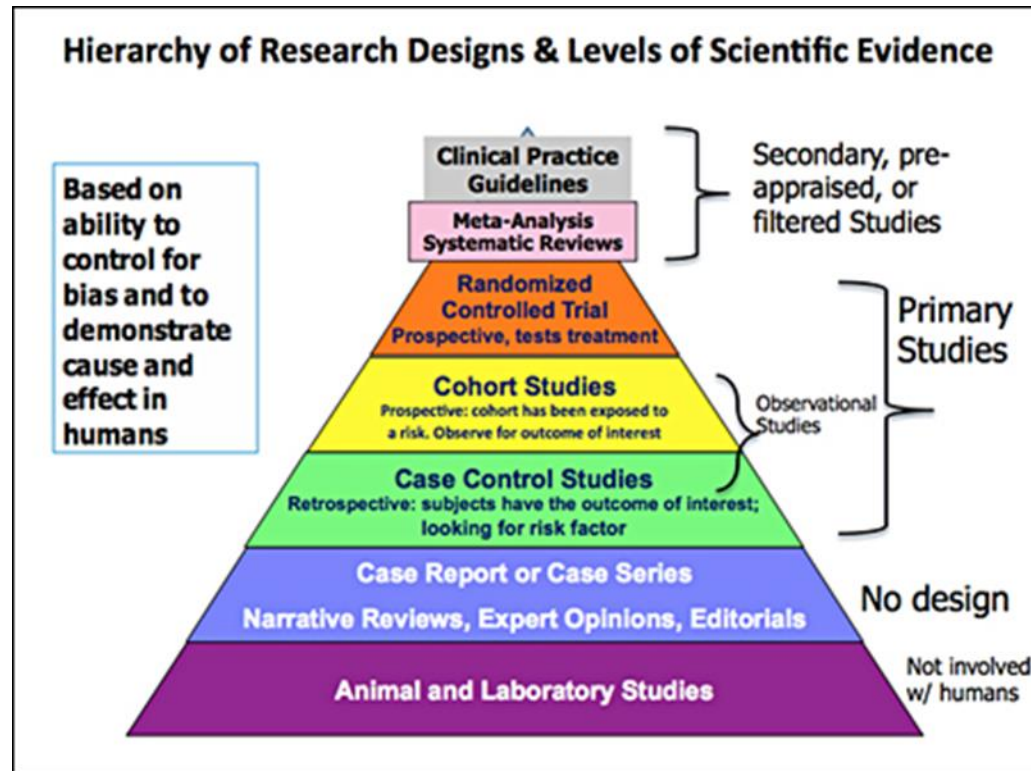
1-Level of evidence:

- Each study design is assessed according to its place in the research hierarchy. The hierarchy reflects the potential of each study included in the systematic review to adequately answer a particular research question, based on the probability that its design has minimised the impact of bias on the results.

What study design is appropriate?

Sterengh of evidence

Level of evidence:



What study design is appropriate?

Sterengh of evidence

2- Research category

Importantly, hierarchies of evidence differ according to research category. For example, if the central clinical issue is ‘prognosis’, a Prospective Cohort Study – not an RCT – is the highest ranked primary study design for this research category.

What study design is appropriate?

Sterengh of evidence

Table 1 NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question (including explanatory notes)

Level	Intervention ¹	Diagnostic accuracy ²	Prognosis	Aetiology ³	Screening Intervention
I ⁴	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among consecutive persons with a defined clinical presentation ⁶	A prospective cohort study ⁷	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among non-consecutive persons with a defined clinical presentation ⁶	All or none ⁸	All or none ⁸	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial ⁹ • Cohort study • Case-control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study ¹⁰ • Interrupted time series without a parallel control group	Diagnostic case-control study ⁵	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ¹¹	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

What study design is appropriate?

Sterengh of evidence

3-Quality of evidence (risk of bias):

- The methodological quality of each included study is critically appraised. Each study is assessed according to the likelihood that bias, confounding and/or chance may have influenced its results.

What study design is appropriate?

Sterengh of evidence

4-Statistical precision:

- The primary outcomes of each included study are evaluated to determine whether the effect is real, rather than due to chance (using a level of significance expressed as a *P*-value and/or a confidence interval).

What study design is appropriate?

- The choice of study design is influenced by a range of factors other than ranking in a hierarchy of evidence, quality and statistical precision. These include **resources** (staff, infrastructure, time, data), **feasibility** and **ethical** considerations.
- The most appropriate quantitative study design for a given clinical research question is dependent upon the **nature of the question** and feasibility of data being asked.

Take home Message

- Clinical trial is not always feasible
- Clinical trial is not always the only way
- Clinical trial is not always relevant
- Clinical trial is not always the best

So when we decide on RCT?

Clinical equipoise

Feasibility

Ethic



با تشکر