Mixed-Method Systematic Review (MMSR): An appropriate method for generating knowledge in rare diseases? Challenges and possibilities

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Background

Conducting systematic reviews on rare diseases implies particular challenges due to: Limited amount of primary studies, studies with few participants, broad focus and covering many issues, and heterogeneity in methodologies, measurement and population.

Objectives

To present key methodologies, results and discuss our experiences of conducting 3 mixed method systematic reviews in rare diseases

- Systematic review of psychosocial aspects of Marfan syndrome MMSR1 (1)
- Systematic review of chronic pain in persons with Marfan syndrome MMSR2 (2).
- Systematic review of quality of life in persons with hereditary thoracic aortic aneurysm and dissection diseases MMSR3 (3)

Systematic searches in databases
MMSR1: 1960 to February 2015
MMSR2: from 1970 to May 2015
MMSR3: from inception to January 2019

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Records screened
MMSR1: 260
MMSR2: 1525
MMSR3: 1220

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Full-text articles considered
MMSR1: n=26
MMSR2: n=151
MMSR3: n=57

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Publications included
MMSR1: n=15
MMSR2: n=20
MMSR3: n=20

Methods

The PRISMA 27-checklist for systematic review was followed (4)

Inclusion:

- Primary studies (all design)
- Reporting on ≥ n=4 participants with relevant diagnosis
- Participants age
- Articles dealing with specific issues
- English, German, French and Scandinavian languages

Method

- Each study was analyzed for primary outcome of reviewed questions
- Thematic analyses for structuring and depicting all relevant articles
- Risk of bias of each paper was assessed by specific criteria (5)
- Two new questions for risk of bias assessement were added for appraisal of studies in rare diseases
- Taking into account methodological quality and the rigors of the studies in the synthesis of the results

Example of quality assessment of studies with quantitative cross-sectional design

Years Authors	HTAAD diagnosis Verified (vd) Not verified (nvd)	1. Study design[1]	2. Representative sample[2]	3. Control groups[3]	4. Qol measure validity[4]	5. Drop out / missing data[5]	6. Discussed limitations[6]	7. Credibility[7]	8. Contribution of quality of life knowledge[8]
Verbraecken et al 2001	MFS (nvd)	Good	Fair/poor	Good	Good	Fair	Good	Fair	Fair
Peters et al 2002	MFS (nvd)	Good/very good	Acceptable/ fair	Acceptable/ good	Good-	Fair/good	Good	Acceptable/ good	Good
Foran et al 2005	MFS (vd)	Good	Good	Good	Acceptable	Poor/fair	Good	Aceptable	Fair/good-
Fusar Poli et al 2008	MFS (nvd)	Good	Fair	Acceptable	Good	Poor	Poor	Fair	Fair
Rand Hendriksen et al 2010	MFS (vd)	Very good/ good	Good	Very good	Good	Fair	Good	Very good	Good

[1] Study design identified and appropriate?
[2] How representative are the study groups for the population?
[3] Is there adequate control group?
[4] Is the validity for measurement acceptable?
[5] Is the study complete with regard to dropout/missing data and reporting respond rate?
[6] Do the authors describe and discuss limitations with the study?
[7] To what extent are study results influenced by factors that negatively impact their credibility?
[8] Does the study contribute to knowledge about QoL in FTAAD?

Ratings: Very good, Good, Acceptable, Fair and Poor

Results

- Most cross sectional studies - no RCT studies or systematic reviews were found
- Studies with small sample sizes (N<200), often without verified diagnosis
- Most studies were from Europe and USA
- Increasing number of studies the last 4 years
- No validated measurement with diagnosis specific scales
- The use of advanced statistics was common despite small study samples
- Studies had different quality of evidence and strength of recommendations

Discussion

- There is an increased research activity on methodological and statistical issues related to rare disorders, but still reviews that include an expedient grading of evidence is far away.
- Due to small amount of research, all types of articles dealing with particular issues can be beneficial to include in the reviews of rare diseases.
- MMSR is a useful and realistic approach for reviewing studies on rare diseases with the possibility of method–pluralism and holistic thinking.
- When the studies are to heterogeneous to perform statistical pooling, including eight criteria for critical appraisal of the studies was useful for assessment of the quality of the studies.

Conclusion

Mixed-Method Systematic Review is appropriate for:

- Surveilling research areas and to systematically assess and summarize publications of low frequency groups and studies with heterogeneity of approaches, methodology and samples.
- Adjusting eligibility criteria for including all types of study designs, due to the small amount of research available, is crucial in rare diseases.
- Both the credibility of the methodological and the results from each study is decisive to assess the studies contribution to new knowledge.

Ref:
1. Mixed Method systematic review of psychosocial aspects of Marfan syndrom. Velvin,G; Bathen,T; Rand-Hendriksen,S ; Østertun Geirdal,A. 2015. Journal of Clinical genetics.
2. Systematic review of chronic pain in persons with Marfan syndrome. Velvin,G; Bathen,T; Rand-Hendriksen,S: Østertun Geirdal,A. 2016. Journal of Clinical Genetics
3. Systematic review of quality of life in persons with hereditary thoracic aortic aneurysm and dissection diseases. Velvin,G; Wilhelmsen,JE; Johansen,H; Bathen,T; Østertun Geirdal,A. 2019 Journal of Clinical genetics
4. http://prisma-statement.org/PRISMAStatement/Checklist.aspx
5. Jack et al 2010. Appraising quantitative research in health education: guidelines for public health educators. Health Promot Pract. 2010 Mar;11(2):161-5.

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