Analysis of an article presenting clinical trial results

EURORDIS MRD Pre-training webinar 2

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Views expressed are mine and do not necessarily constitute ABPI policy

Article analysis

- What are the challenges of clinical trials for rare diseases highlighted in the article?
- What are the good points of the study conducted? What were the weaknesses?
- What data is included and what is not/what is missing that would have been interesting to know?

Articles

Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): an international, multicentre, open-label, randomised controlled trial

Lakshminarayan R Ranganath, Eftychia Eirini Psarelli, Jean-Baptiste Arnoux, Daniela Braconi, Michael Briggs, Anders Bröijersén, Nadia Loftus, Helen Bygott, Trevor F Cox, Andrew S Davison, Jane P Dillon, Michael Fisher, Richard FitzGerald, Federica Genovese, Helena Glasova, Anthony K Hall, Andrew T Hughes, Juliette H Hughes, Richard Imrich, Jonathan C Jarvis, Milad Khedr, Dinny Laan, Kim-Hanh Le Quan Sang, Emily Luangrath, Oľga Lukáčová, Anna M Milan, Alpesh Mistry, Vanda Mlynáriková, Brendan P Norman, Birgitta Olsson, Nicholas P Rhodes, Jozef Rovenský, Mattias Rudebeck, Annalisa Santucci, Ella Shweihdi, Ciarán Scott, Jana Sedláková, Nicolas Sireau, Roman Stančík, Johan Szamosi, Sophie Taylor, Christa van Kan, Sobhan Vinjamuri, Eva Vrtíková, Chris Webb, Elizabeth West, Elizabeth Záňová, Andrea Zatkova, James A Gallagher

Summary

Lancet Diabetes Endocrinol

Background Alkaptonuria is a rare, genetic, multisystem disease characterised by the accumulation of homogentisic

How to get warmed up with your reading

1. How do you find an article that you might be interested in?
2. How are you reassured it is robust and of high quality and worth your time?
3. What is the journal? impact factor? Does it matter?
4. What makes a good Title?
5. Who are the authors?
6. Abstract should tell you whether to go deeper

   - Why shouldn't you rely on it for your conclusions?

Next steps - introduction

- Introduction should provide relevant information on the condition and research setting – also provides key background information from the author's perspective
- What important information does it tell you about the surrogate marker? (clinical trial endpoint used as a substitute for a direct measure of how a patient feels, functions, or survives)
- Scientific rationale for why this study should take place
- Provides background on an inconclusive study
- Need to carefully review all evidence – build the next stage such as dosing requirement - often missing in repurposing

Next steps – methods

- Methods – essential to read
  - Why randomise? Why blind if you can?
  - Acceptability of no treatment control
  - Study sites – France, UK and Slovakia (+Jordan)
  - Primary endpoint is a biochemical surrogate endpoint - relevance to patients?
  - Age - over 25 years
  - Challenges in recruitment 19 patients from Jordan
  - Statistical analysis – normally need expert input

Next steps - results

- Participant flow – tells the story of the trial recruitment and retention

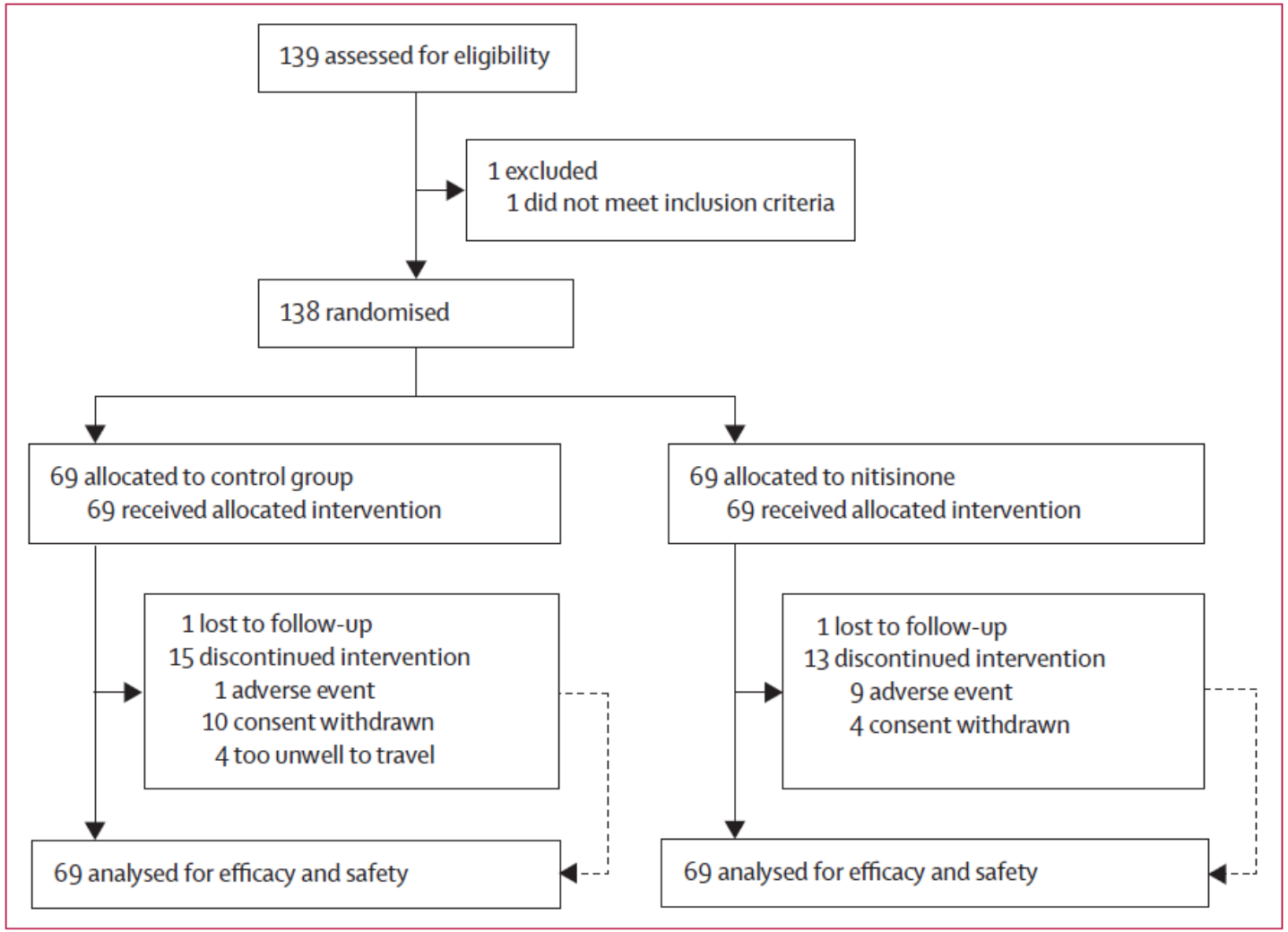


Figure 1: Trial profile

Next steps - results

- Base characteristics – tells you who was in the study – is it representative?

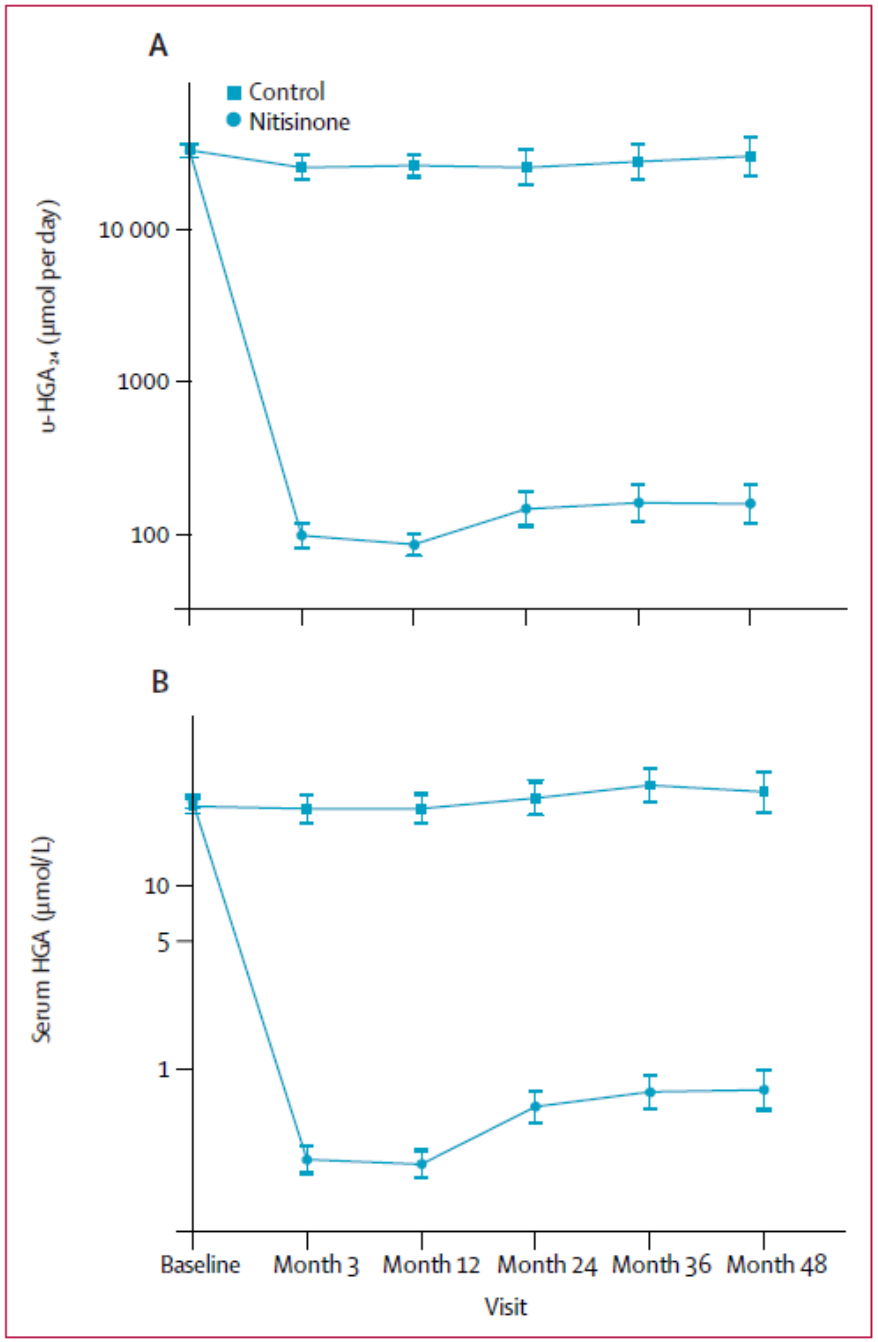
	Control (n=69)	Nitisinone (n=69)	Total (n=138)
Age, years	47·6 (10·1)	49·0 (11·3)	48·3 (10·7)
Bodyweight, kg	74·1 (15·6)	74·8 (14·8)	74·4 (15·1)
Height, cm	167 (9·5)	166 (9·2)	167 (9·4)
Sex			
Female	29 (42%)	24 (35%)	53 (38%)
Male	40 (58%)	45 (65%)	85 (62%)
Race			
White	67 (97%)	67 (97%)	134 (97%)
Black	0	1 (1%)	1 (1%)
Asian	2 (3%)	1 (1%)	3 (2%)
Study centre			
Liverpool, UK	21 (30%)	20 (29%)	41 (30%)
Piešťany, Slovakia	32 (46%)	33 (48%)	65 (47%)
Paris, France	16 (23%)	16 (23%)	32 (23%)

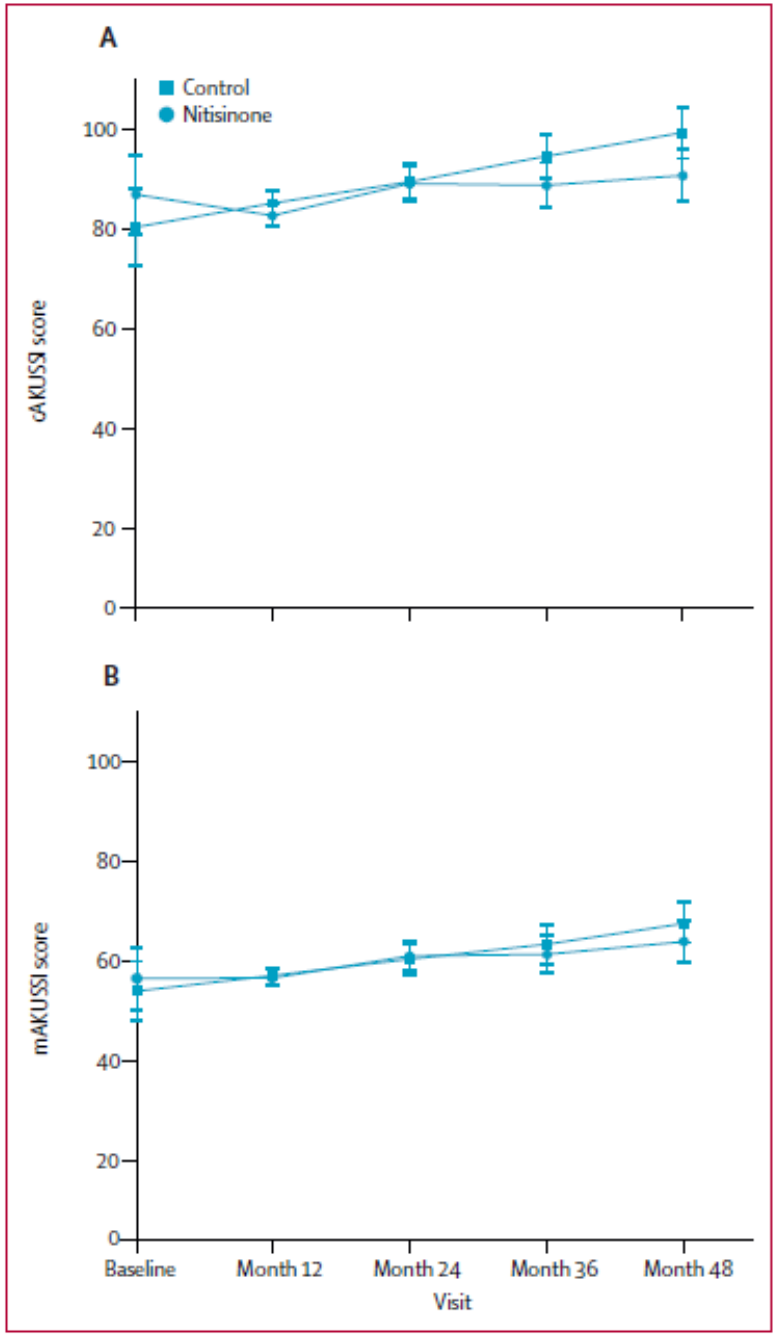
Data are mean (SD) or n (%).

Table 1: Demographic data and baseline characteristics

Next steps - results

- Looks impressive?
- Look at the scales
- Statistically significant versus surrogate versus clinically relevant?
- Watch out for subgroup analysis and over interpretation





Next steps - results

- Don’t forget safety and tolerability
- Studies nearly always powered for efficacy
- Safety signals problematic in small populations
- Study drug related events
- Discontinuations?

	Control (n=69)		Nitisinone (n=69)	
	Number	Incidence per 10 patient years	Number	Incidence per 10 patient years
Patients with at least one adverse event	57 (83%)	2·1	59 (86%)	2·3
Adverse events	284	..	400	..
Patients with at least one serious adverse event	26 (38%)	1·0	27 (39%)	1·0
Serious adverse events	52	..	57	..
Patients with at least one study drug-related adverse event*	NA	NA	18 (26%)	0·7
Study drug-related adverse events*	NA	..	48	..
Deaths	0	0·0	2 (3%)	0·1
Patients with adverse events leading to study discontinuation	1 (1%)	0·0	9 (13%)	0·3
Patients with adverse events leading to dose reduction	NA	NA	8 (12%)	0·3

Data are number of events or n (%) unless indicated otherwise. NA=not applicable. *Adverse event was judged to be related to the study drug by the investigator.

Table 3: **Adverse events**

Next steps – Discussions etc

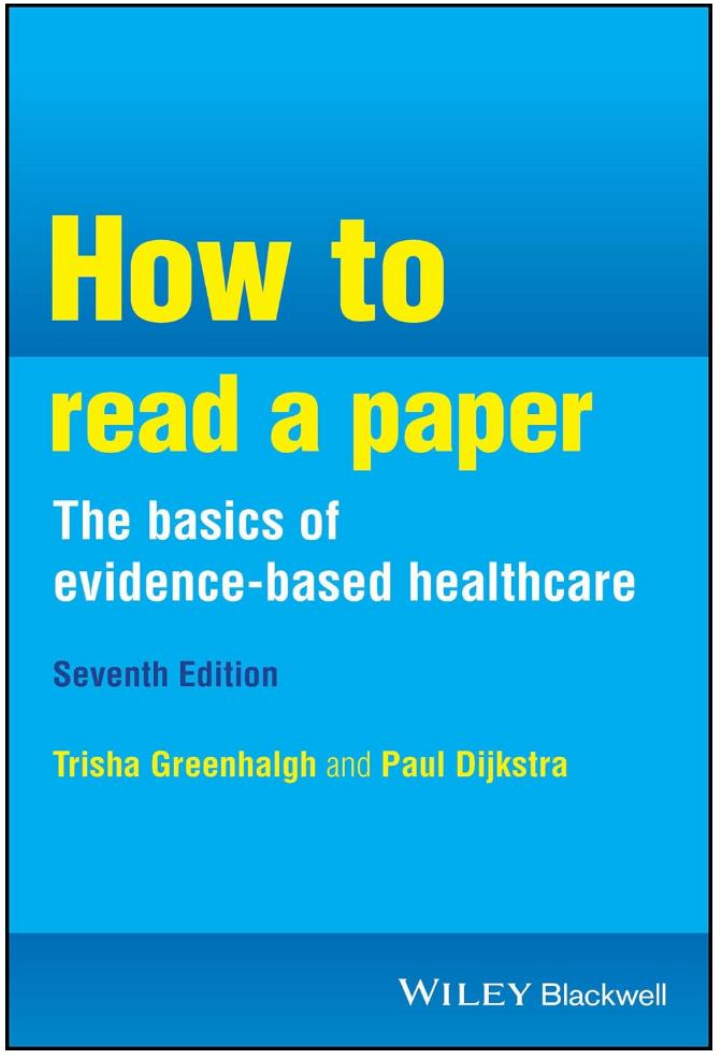
- Discussion should be balanced and critical – not always
- Lancet has Research in Context – useful perspectives
- Don’t forget to look at the declaration of interest – why?
- References can be helpful for your next read!

References

- Highly recommend: How to Read a Paper: The Basics of Evidence-based Medicine and Healthcare, Trisha Greenhalgh - 2024

- ICH guidelines - ICH Official web site : ICH – efficacy guidelines concerned with the design, conduct, safety and reporting of clinical trials

- Finding paper – pubmed search engine - PubMed (nih.gov)



Q&A