Legislation, guidelines and regulations for in vitro diagnostic tests in the UK: a scoping review

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The aim of our research project has been to describe the legislation, guidelines, and recommendations applicable to new diagnostic and screening tests brought to market in the United Kingdom as of 01/06/23.

The review sought to identify sources and extract agreements, disagreements, and gaps in recommendations. We also have carried out a thematic analysis to look at issues identified by stakeholders with the new set of regulations that are being proposed.

Introduction

In vitro diagnostic tests have a significant role in making healthcare decisions and therefore have to be reliable, safe and accurate. Therefore, well-developed regulations are required to ensure that tests meet these criteria. UK regulations are currently based on the Medical Devices Regulations 2002, however, new regulations are planned, proposed to be similar to the new European in vitro diagnostics regulations (IVDR) introduced in 2017, applied from May 26th 2022. As the UK regulations are under review, it is important to understand the current regulatory landscape, and any areas which require improvement.

Objective

We aimed to answer the following questions:

- What is considered a new in vitro diagnostic test and how are they classified?
- What is the current process for regulatory approval for each class of in vitro diagnostic tests, including direct-to-consumer testing?
- What other applicable legislation, guidelines and recommendations are extant?
- How do different legislation, guidelines and recommendations on each diagnostic test agree and disagree?

Methodology

The scoping review has been conducted in accordance with the JBI methodology for scoping reviews.

We conducted a preliminary web-based search using terms for relevant regulations (in vitro diagnostic regulations AND UK OR Europe). We decided to search both published and unpublished literature, as there may be guidelines and other recommendations published that will not appear when searching peer-reviewed literature. Abstracts and titles were analysed to identify keywords and search terms of relevance.

We agreed on the follwing search strategy:

KEYWORD	ALTERNATIVES
IN VITRO DIAGNOSTIC	IVD OR diagnostic test OR direct to consumer test
Regulat*	Standardization OR approval OR certif* OR validation OR medical device legislation
UK OR EU	United Kingdom OR Europe

We extracted the following data from the identified relevant articles: date of publication, source, authority (legal, guidance or recommendation), types of tests covered, test performance requirements, applicability (population covered), recommendations, theme, paper type, conflicts of interest and the country of origin.

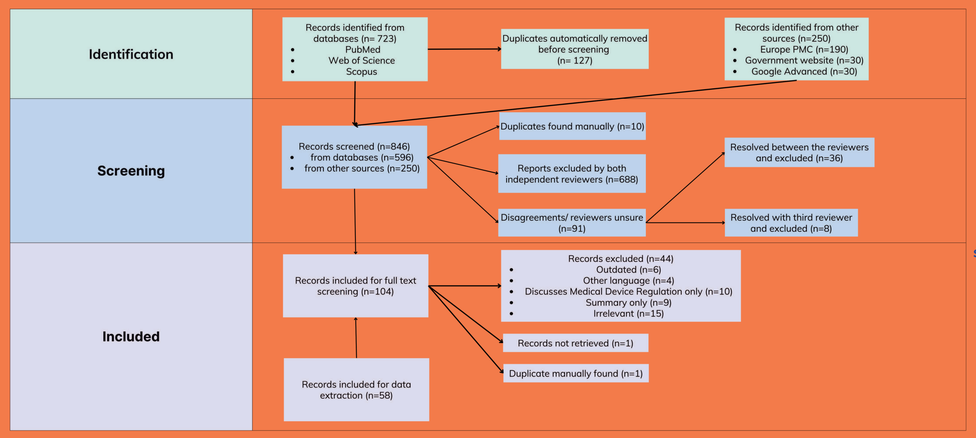

Figure 1. Flow diagram showing the screening process.

Related literature

- The Medical Devices Regulations 2002. Available from: https://www.legislation.gov.uk/uksi/2002/618/contents/made
- EU IVDR. Available from: https://eur-lex.europa.eu/eli/reg/2017/746/oj
- Ashby D, Bird S, Deeks J, Evans S, Perera R, Takwoingi Y, et al. Royal Statistical Society Diagnostic Tests Working GroupReport. Royal Statistical Society; 2021 June 2021.

PROTOCOL LINK

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Preliminary Analysis

We have decided to use thematic analysis to find the common themes within the research produced about the legislation. We identified any sub-themes within the data and then combined these into overall themes.

The graph below represents how often these themes came up in the data, and two key themes were identified: issues with transitioning to the new set of regulations, primarily due to a concern about lack of capacity to conformity assess tests, and the other key theme is concerned about laboratory developed tests (LDTs) being overregulated.

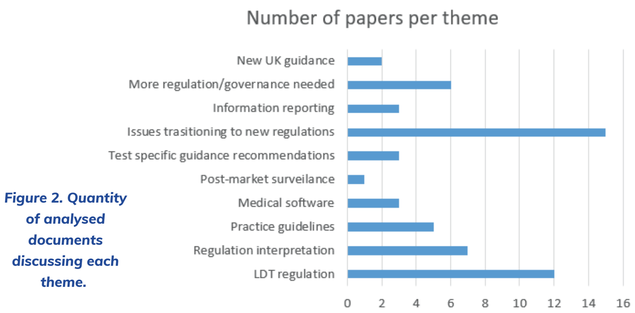

Figure 2. Quantity of analysed documents discussing each theme.

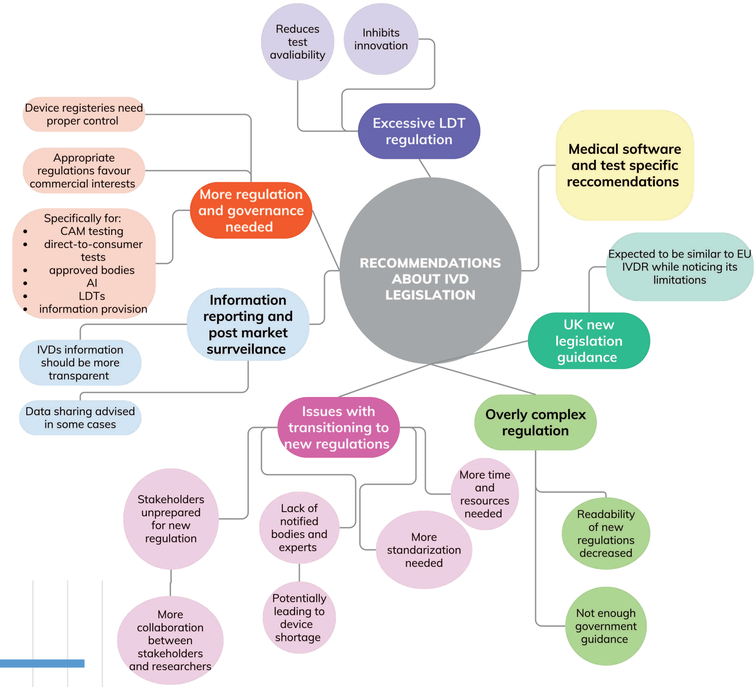

Figure 3. Mind map showing the identified themes and subthemes regarding suggestions and concerns about IVD legislation.

Conclusion

In conclusion, the data extracted so far unveiled a spectrum of recommendations, opinions and suggestions on future of IVD regulations in the UK. Insights so far give valuable guideposts for different stakeholders. Although mainly focusing on the established EU IVDR, the literature highlights shortcomings, including issues with transitioning to new regulations, excessive LDT regulation but more governance needed in other areas. Identification in order to address these is necessary for successful formulation and implementation of future diagnostic tests' legislation.

DATA EXTRACTION SPREADSHEET

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Further work

- The scoping review is not yet complete and the analysis is not yet finalised. We are planning to complete the thematic analysis, and also look at the conflicts of interest in each article. We will then compare how this relates to the themes, and if there is any link between how the research has been funded, and whether a paper is calling for more or less regulation for example.
- A future systematic review in this area could be planned based on the evidence we have found.

Use of multiplex immunofluorescence labelling to characterise ion channel expression in the distal nephron

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Background

- The kidneys contribute to the long-term control of blood pressure by regulating our extracellular fluid volume. This is achieved by tightly controlling total body sodium balance e.g. Na^+ excretion must equal Na^+ intake.
- The critical fine-tuning of Na^+ balance takes place in the distal nephron through the actions of various hormones, including corticosteroids such as aldosterone (ALDO) and cortisol, which modify Na^+ transport processes[1].
- The distal nephron, in particular the collecting duct (CD), is thought to be aldosterone-sensitive due to the activity of an enzyme 11βHSD2, which converts the more abundant cortisol to an inactive metabolite.
- Recent data has reported an ALDO-insensitive portion of the nephron[2] where basal ENaC activity is high, with the suggestion that ENaC appears earlier in the distal nephron in the absence of 11βHSD2.
- However, where this ALDO-insensitive ENaC localises, e.g. alongside the thiazide-sensitive Na^+-Cl^- co-transporter (NCC) in the distal convoluted tubule (DCT), or in the connecting tubule (CNT) with TRPV5, remains unclear.

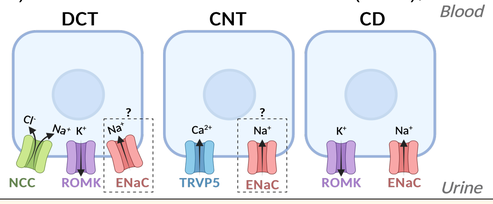

Fig 1. *Apical ion transporters involved in Na^+ reabsorption in the distinct segments of the distal nephron: distal convoluted tubule (DCT); connecting tubule (CNT); and collecting duct (CD). NCC – Na^+-Cl^- co-transporter, ROMK – renal outer medullary K^+ channel, TRPV5 - transient receptor potential vanilloid 5 cation channel, ENaC – epithelial Na^+ channel. Figure modified from (1).*

Aim

- To develop a method to quantitatively characterise the expression of the transporters of the distal nephron in mouse kidney.

Methods

- Ion channels were labelled using multiplex immunofluorescence (IF) of formalin-fixed paraffin-embedded kidney sections from wild-type (WT) and 11ßHSD2-knockout (11ßKO) C57BL/6 male mice (Fig. 2).

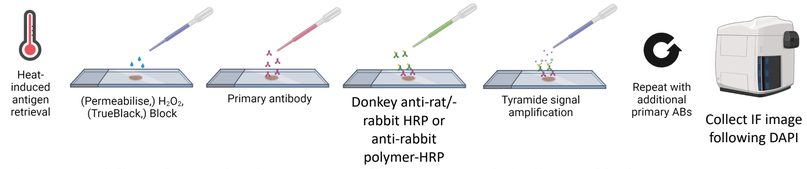

Fig 2. *Workflow for multiplex immunofluorescence labelling of kidney sections.*

- Sections were permeabilised, peroxidase activity was quenched, and background autofluorescence reduced with TrueBlack incubation.
- Non-specific binding was prevented by blocking with either 10% NDS or non-serum block.
- Sections were labelled sequentially with 3 primary antibodies TRPV5/NCC/γ-ENaC or ROMK/NCC/γ-ENaC, each with their respective HRP-conjugated secondary antibody and incubated with a fluorophore-linked tyramide signal amplication dye e.g. FITC, Cy3, Cy5. DAPI was used as a nuclear counterstain.
- IF images were captured and the initial triple-labelled sections were analysed using *Halo*® software.
- Nuclei were identified in the images and used to train AI nuclear segmentation. A cytoplasmic 'ring' around the nuclei was then set.
- Positive controls for each channel were annotated, consisting of around 200 cells, and negative controls for the three channels were annotated, consisting of around 600 cells (Fig. 3).
- These annotations then enabled the generation of a positive and negative threshold for each channel per image (Fig. 4).

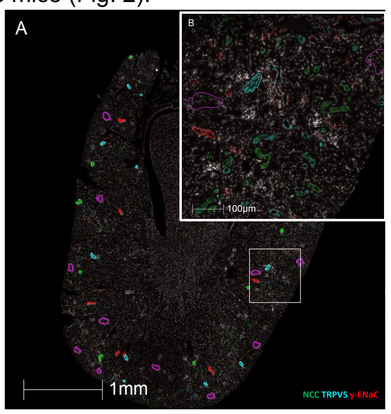

Fig 3. *IF image of (A) whole kidney showing annotations to define positive and negative labelling. (B) higher magnification of selected area.*

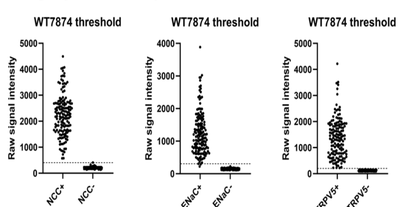

Fig 4. *Example of thresholds set for cells positively labelled for each ion channel.*

Results

Quantification of NCC/TRPV5/γ-ENaC expression in WT mouse kidney

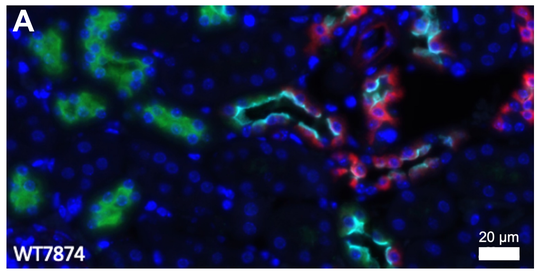

Fig 5. *(A) Representative image of NCC/TRPV5/γ-ENaC labelling in a WT kidney section. Scale bar denotes 20 µm. (B) Chart showing proportion of single/double/labelled cells (n=3).*

- Of the single labelled cells, γ-ENaC+ cells were the most abundant (~40% of labelled cells), then NCC+ (~23% of labelled cells) and then TRPV5+ (~3% of labelled cells).
- TRPV5 showed more co-localisation with γ-ENaC+ (~23% of labelled cells) than NCC+ (~6% of labelled cells).
- There was a low abundance of cells expressing both NCC and γ-ENaC (~1% of labelled cells), and triple+ cells expressing all 3 channels/transporters (~3% of labelled cells).

Expression of NCC/TRPV5/γ-ENaC in 11ßKO and ROMK/NCC/γ-ENaC expression in WT kidney sections were investigated qualitatively

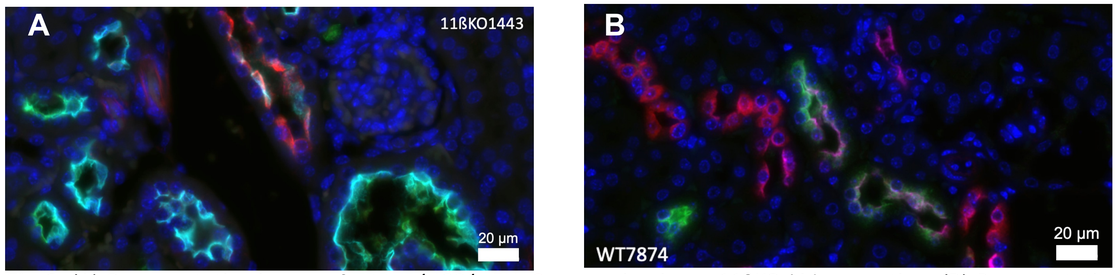

Fig 6. *(A) Representative image of TRPV5/NCC/γ-ENaC expression in an 11ßKO kidney section. (B) Representative image of ROMK/NCC/γ-ENaC expression in a WT kidney section. Scale bar denotes 20 µm.*

- In 11ßKO tissue, the DCT was hyperplastic and hypertrophic, γ-ENaC was more apically expressed, and the connecting tubule was more prevalent.
- In ROMK/NCC/γ-ENaC-labelled WT tissue, a large proportion of cells expressing NCC/γ-ENaC also expressed ROMK.

Conclusions

- Established a method to quantitatively characterise NCC/TRPV5/γ-ENaC expression in FFPE kidney sections.
- Generated data demonstrating the relative expression of single/double/triple-labelled cells of the distal nephron.
- Investigated NCC/TRPV5/γ-ENaC expression in 11ßKO and ROMK/TRPV5/γ-ENaC in WT kidney sections.

Acknowledgements and Funding

- Thank you to Dr Morag Mansley, Struan Loughlin and Morag Milne for their training, guidance and support throughout my studentship. Thank you to the Harrison Group for allowing access to their slidescanner and Halo software, Dr. In Hwa Um for help with Halo image analysis and John O'Connor for cutting the kidney sections used. Thank you to Dr. Rob Hunter (The University of Edinburgh) for providing the kidney tissue used.
- This studentship was funded by the Society for Endocrinology.
- *Fig 1.* was created with BioRender.com.

References

1. Pearce, D et al. (2022). Pflugers Arch **474**: 869-84
2. Nesterov, V et al. (2021). Amer J Physiol Renal Physiol **321**: F257-268

Where Do GPs Get Their Information Online?

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Introduction

GPs often need to consult resources to answer clinical questions. Recently, there has been a shift from using physical to online resources. There is a huge range of resources available online, and their reliability varies depending on funding, conflicts of interest and their evidence base, which will influence clinical decisions made by GPs in practice (McCartney, M, 2022).

Project Aims

This is an exploratory project looking at online clinical decision tools used by GPs.

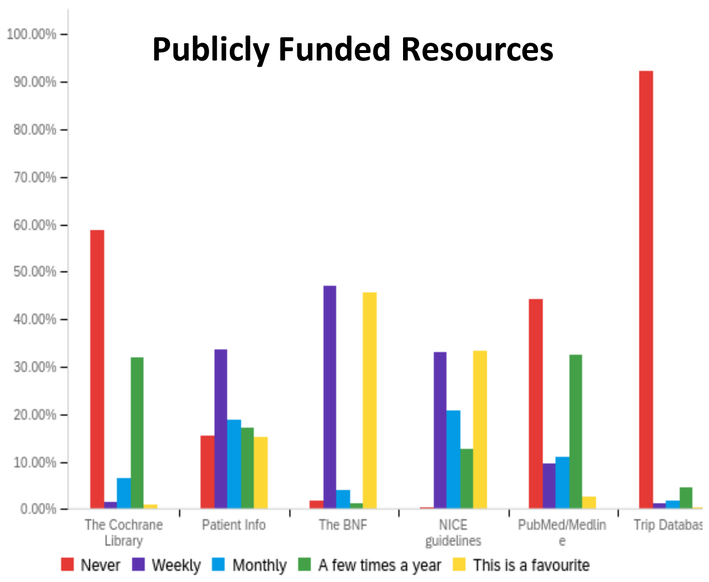
- Map where GPs are finding their information online
- Analyse the reliability of each resource, looking specifically at funding, conflicts of interest and evidence bases

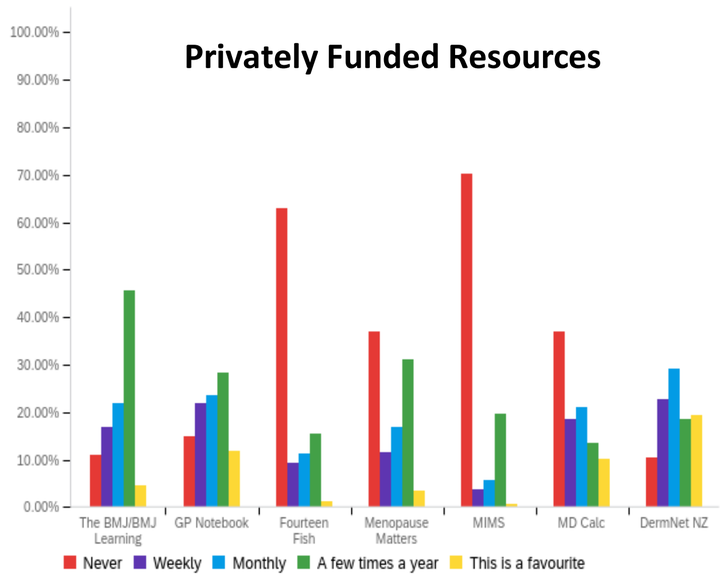
Methods

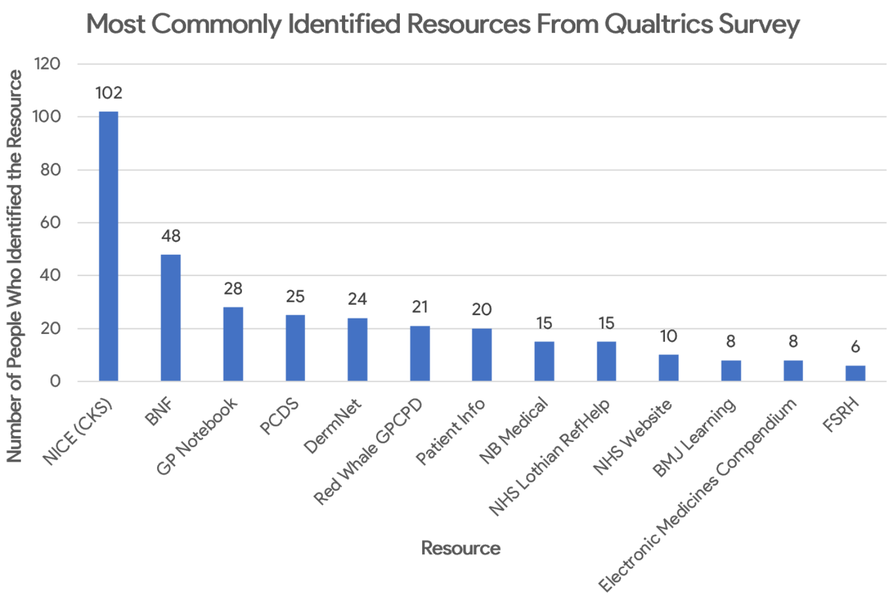
A survey was distributed to GPs via Twitter, which asked participants how often they used a selection of 13 publicly and privately funded resources. These were analysed looking at funding, pharmaceutical influence, conflicts of interest and evidence base.

Results

The survey received a total of 336 responses, 280 of which were from GPs. The results are shown on the graphs below.







There are a huge number of resources available online for GPs.

Over 150 resources were identified from the survey. Therefore, which resources are most appropriate for GPs to use to answer clinical questions?

The survey identified a number of "favourite" resources amongst the participants, the most popular being the BNF, NICE guidelines, Patient Info and Dermnet NZ. These were a mix of privately and publicly funded resources and aimed at GPs and patients.

Some resources with public funding are not commonly used by GPs.

Most of the favourite resources were publicly funded, but some of the less common resources were also publicly funded. Therefore, why aren't these resources being used by GPs? This leads us to wonder whether these resources are targeting the most common clinical queries in general practice. Should this funding be used for more commonly used resources?

Many resources with pharmaceutical funding are regularly used by GPs.

Some popular resources are partly funded by corporate sponsorships and pharmaceutical companies, such as Dermnet NZ. Many of these are ambiguous about conflicts of interest, raising concerns about bias as these resources are not as easily regulated as public ones. This raises questions about the impact this could have on patient care.

Conclusion

The results raised several questions about which resources should be used to answer clinical questions, especially when there are so many resources available online and many of those may have conflicts of interest due to pharmaceutical funding. The data also led us to question why some publicly funded resources aren't being used and whether this funding should go elsewhere to develop resources targeted towards more common clinical questions.

Scan here to see our results

References

McCartney, M., 2022. Modern Mindlines in primary care [WWW Document]. URL osf.io/7jzsm
Gabbay, J. and May, A. le (2004) 'Evidence based guidelines or collectively constructed "mindlines?" ethnographic study of knowledge management in Primary Care', BMJ, 329(7473), p. 1013. doi:10.1136/bmj.329.7473.1013.
Google Logo, google.co.uk

This project builds on the project with data previously started by Kate Connolly, Brid Hendry and Yu Heng Ho, under the supervision of Dr Margaret McCartney

Does treatment with corticosteroid and/or antiviral therapy alter time to complete recovery in cases of idiopathic, unilateral, peripheral facial nerve paralysis ?

Researcher: William Kingston
Supervisors: Professor Fergus Daly and Professor Frank Sullivan

Background

Bell's palsy affects up to 40 people per 100,000 population annually.[1] The disease is usually transient, and most patients recover within a year. Research has been conducted focusing on corticosteroids and antiviral treatments to establish if they provide benefit to the overall recovery probability but there remains a lack of clarity regarding duration of disease. This research project focuses on time to recovery with an aim to establish a better understanding of the effect treatment can have on the duration of disease.

Aim

The aim of this research project was to establish timelines for recovery from the symptoms of Bell's palsy depending on treatment allocation to aid patient understanding of the disease and treatment options.

Methods

The data sets from the two largest Bell's palsy studies were combined. Using Microsoft Excel this merged data set (n=1325) was examined to explore differences in overall recovery rate between treatment groups. The four groups for comparison were groups AP, AO, OP, OO (A-Antiviral, P-Prednisolone, O- Placebo). Data was presented in the form of dates of assessment and the grade given according to the House-Brackmann facial grading scale. Intervals were created for each patient bounded by the last day they were assessed as unwell and the first day they were assessed to be well.

Kaplan-Meier plots were generated for upper and lower bounds of the recovery intervals (Figures 1a&b). These gave upper and lower bound probabilities of recovery with relation to time after treatment allocation.

Probability modelling was used to create curves for recovery probability against time for the four treatment groups (Figure 2). The modelled point data for median days to recovery allows comparison of the effect treatment has on speed of recovery. Timelines (Figure 3) were created from the model using the recovery probability on specific days (30, 60, 90, 120, 300, 360).

Results

From Kaplan-Meier plots: Steeper gradients of the traces for treatment groups with prednisolone indicates a greater speed of recovery with corticosteroid than without. Indistinguishable results between groups AP and OP suggest that addition of antiviral to prednisolone has no benefit. Similarly indistinguishable results between groups AO and OO suggest that treatment with antiviral has no benefit over placebo treatment.

From Probability Model: Treatment with prednisolone gives a large improvement in recovery time compared to those without corticosteroid ($p<0.0001$). Treatment with antiviral has no effect on recovery time compared to those not treated with antiviral ($p = 0.571$).

Discussion

This research project has shown that treatment with corticosteroid does reduce the duration of symptoms of Bell's palsy. Our analyses failed to demonstrate any benefit or detriment of additional therapy with antivirals. Timelines of probability of recovery produced aid understanding of the disease and can help patients and clinicians consider treatment options.

Prednisolone reduces duration of symptoms with Bell's palsy and improves recovery likelihood with time.

Full Report for more Information

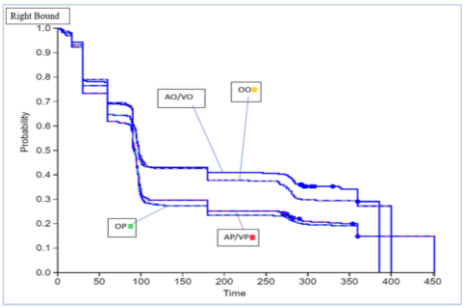
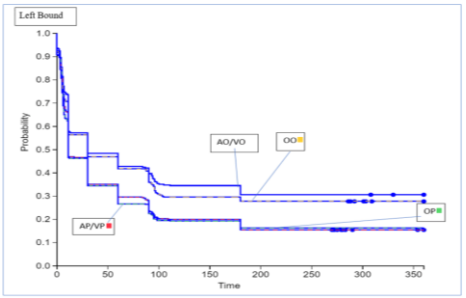


Figure 1a&b: Kaplan-Meier plots from merged data set. Failure to recover is displayed as 'Survival'.



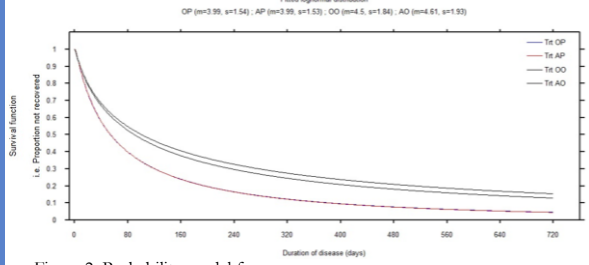


Figure 2: Probability model for recovery

Figure 3a: A timeline of recovery probability from the lognormal probability model for the OP treatment group. Recovery probability rounded down to 2 s.f.

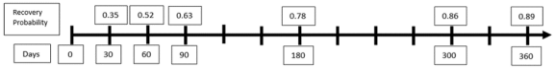


Figure 3b: Timeline for AP group

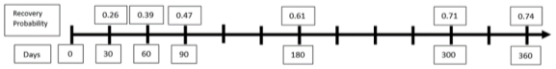


Figure 3c: Timeline for AO group

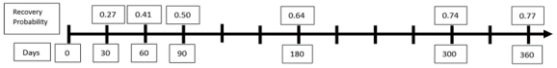


Figure 3d: Timeline for OO group

1. Holland NJ, Bernstein JM. Bell's palsy. BMJ Clin Evid [Internet]. 2014 [cited; 2014.
2. Kaplan-Meier plots generated with: Rosenmai P. Kaplan Meier Survival Curve Grapher Eureka Statistics 13 Jan 2015.