

## Future Research in Graves' Orbitopathy: From Priority Setting to Trial Design Through Patient and Public Involvement

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**G**RAVES' ORBITOPATHY (GO) is a disfiguring autoimmune condition, which can sometimes cause blindness (1). The disease has profound effects on quality of life (2), psychological health (3), and socioeconomic status (4). Progress in understanding and treating this disease has been slow. However, recent advances include delineation of plausible immunological mechanisms (5), development of an animal model (6), and publication of randomized studies defining the role and limitations of intravenous steroids (7), rituximab (8,9), and selenium (10). Yet, some of this knowledge remains to be translated into improvement in clinical care. Access of patients to specialist treatments is patchy and seems to depend on chance rather than clinical need (11). In 2009, 84 international, national, scientific, and patient-led organizations signed the Amsterdam Declaration for people with Thyroid Eye Disease (12). Signatories pledged to "improve the existing research networks and develop further international collaborative research."

Patient and public involvement (PPI) is increasingly recognized as an important and positive influence in research (13). Research funding organizations often require that applicants provide evidence of PPI in research proposals. In 2012, the first ever PPI event for inflammatory ocular diseases was organized by the Moorfields National Institute for Health Research Biomedical Research Centre in London,

United Kingdom, overseen by the James Lind Alliance (14). This resulted in setting priorities for future research in inflammatory ocular conditions (15).

Here, we share our further experience with PPI leading to refinement of the priorities for future research, and translation into answerable research questions and study design outlines, through a two-day event. The event was planned by a committee representing professional and patient-led organizations (16,17). It was publicized in the media (newspaper, municipal Web sites on events, newsletters, general practitioner surgeries, patient organizations, professional organizations). Attendees registered as members of the public if they were not patients with thyroid disease or health professionals. Day 1 was aimed at patients, the public, experts, and professionals. It included an introductory session about GO for patients and the public, patient testimonies about their experience with the disease, and a breakout session into three working groups. Day 2 consisted of a scientific meeting aimed at professionals and six invited expert patients. It included reviews of the pathogenesis and clinical management of GO, highlighting recent advances in these areas. It was followed by a breakout session of three working groups for professionals, experts, and expert patients, allocated to translating the selected research questions formulated in breakout session 1, to study design outlines. The

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objectives of breakout session 1 were to discuss six questions per group previously set by the Sight Loss and Vision Priority Setting Partnership (15) and select a maximum of two questions per group based on scientific merit and relevance to unmet patient needs (Fig. 1). The chair and co-chair for each group were asked to use the PICO (patient, intervention, comparator, outcome) principle (18) in order to formulate the selected research questions for further elaboration in breakout session 2 on day 2. Groups in breakout session 2 consisted of a chair, co-chair, expert panelists (including two expert patients per group) and professionals. They were asked to discuss and translate the PICO questions of breakout session 1 into study designs.

The event was successful in drawing a sizeable (147 on day 1 and 131 on day 2) and diverse audience (public, patients, endocrinologists, ophthalmologists, and basic scientists from 13 different countries), and met the previously set targets for attendance and participant mix by the organizing committee. PPI was achieved as judged by the number of people who attended and the significant influence exerted by patients and the public on selection and direction of potential studies. The outcomes from breakout sessions 1 and 2 are shown in Figure 1 and Table 1. The net cost of the meeting (total cost minus registration fees) was £18,000 (\$28,300).

The selection of psychological intervention as one of the priorities was not anticipated by the authors, but clearly this is of great interest to patients and the public, and it has now been documented as an unmet need worthy of future research. What also emerged as a priority was the importance of

developing a method for predicting the development of GO with a high degree of accuracy. The number of patients with GO seems to be declining (19), and we anticipate that the emphasis of future interventions will be in prevention. In order to conduct meaningful randomized controlled trials, there is a need to target patients with Graves' disease who have no clinical expression of GO at the time of recruitment but are likely to develop the disease, and such a study was given high priority.

In conclusion, we were able to conduct a successful PPI event on GO, which prioritized 6/16 previously set research questions, and translated them into four outlines of study designs, two of which emerged as highest priorities. Unmet patient needs informed and guided the selection process. This will provide strong evidence of PPI in future bids by the thyroid community for funding these studies, and may be a useful model for PPI in research planning and prioritization for other thyroid diseases.

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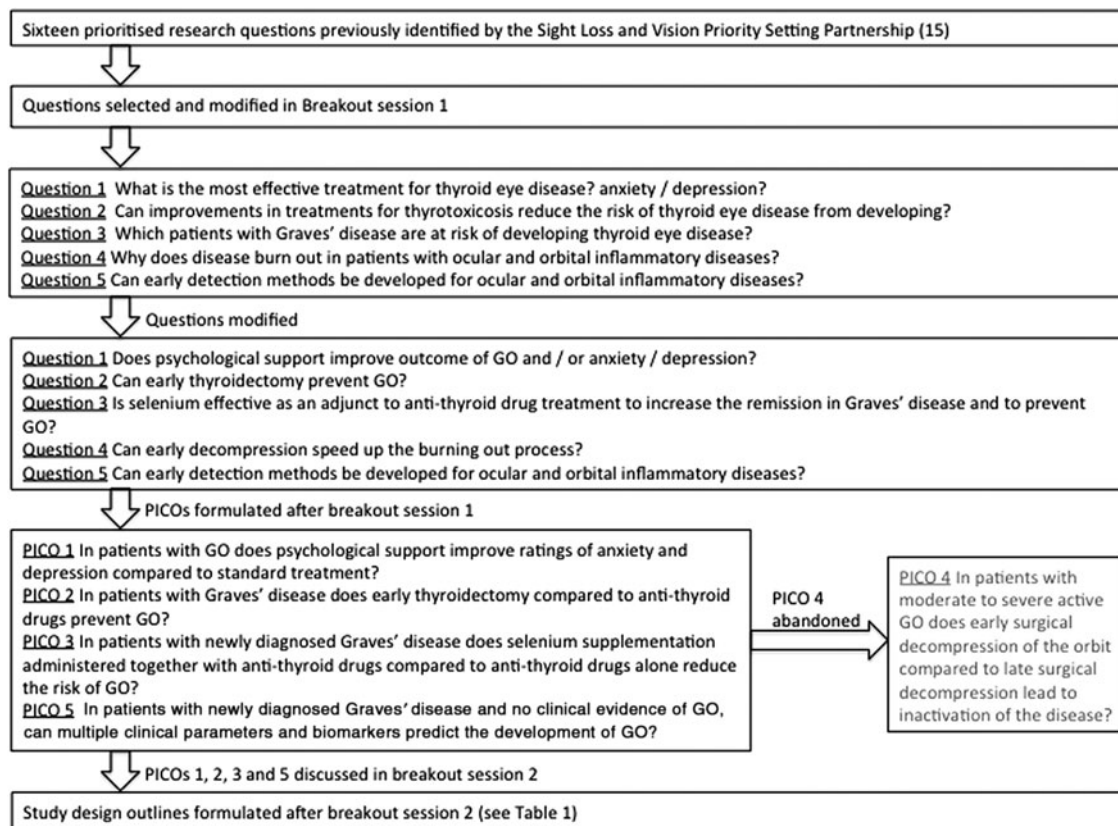


FIG. 1. Flow diagram outlining the processes for prioritization and formulation of research questions.

TABLE 1. STUDY DESIGN OUTLINES PROPOSED

Study identification	PICO	Study title/aim	Design	Setting/duration of follow-up	Inclusion criteria	Intervention	Assessments	Primary outcomes
A	PICO 1: In patients with GO, does psychological support improve ratings of anxiety and depression compared to standard treatment?	<b>Title:</b> Psychological support in GO <b>Aim:</b> To determine the effect of psychological support on psychological well-being and quality of life	Prospective, randomized, single blinded	<b>Setting:</b> Multiple tertiary centers <b>Duration of follow-up:</b> 1 year	Patients with new onset GO, scoring above a predetermined threshold using a tool such as the Hospital Anxiety and Depression Scale	Formal psychological intervention (such as cognitive behavior therapy) versus standard care	Demographics, history, clinical/ophthalmological assessments (20), questionnaire-based measures of psychological well-being and quality of life (2) at baseline and at the end of the intervention period	Questionnaire-based measures of psychological well-being and quality of life (2)
B	PICO 2: In patients with Graves' disease, does early thyroidectomy compared to antithyroid drugs prevent GO?	<b>Title:</b> Early total thyroid ablation in prevention of GO <b>Aim:</b> To determine whether total thyroid ablation prevents the development of GO	Prospective, randomized single blind design	<b>Setting:</b> Multiple endocrine clinics with access to tertiary centers <b>Duration of follow-up:</b> 1 year	Newly diagnosed patients with Graves' disease without GO who are at high risk of developing GO	Total thyroid versus antithyroid drugs	Assessments and follow-up as described in Leo <i>et al.</i> (21)	Rate of new onset of GO
C	PICO 3: In patients with newly diagnosed Graves' disease, does selenium supplementation administered together with antithyroid drugs compared to antithyroid drugs alone reduce the risk of GO? PICO 4: In patients with moderate to severe active GO, does early surgical decompression of the orbit compared to late surgical decompression lead to inactivation of the disease?	<b>Title:</b> Prevention of GO with selenium <b>Aim:</b> To determine whether selenium supplements prevent GO  Abandoned	Prospective, randomized, double-blinded study	<b>Setting:</b> Multiple endocrine clinics with access to tertiary centers <b>Duration of follow-up:</b> 1.5 years	Newly diagnosed patients with Graves' disease and no GO and low serum selenium	Selenium supplements 200 µg daily with antithyroid drugs versus antithyroid drugs only	Demographics, history, clinical/ophthalmological assessments (20)	Development of GO, and disease-specific quality of life assessments (2)
D	PICO 5: In patients with newly diagnosed Graves' disease and no clinical evidence of GO, can multiple clinical parameters and biomarkers predict the development of GO?	<b>Title:</b> Prediction of GO <b>Aim:</b> To determine whether clinical parameters and GO in patients with Graves' disease	Prospective, observational study	<b>Setting:</b> Multiple endocrine clinics with access to tertiary centers <b>Duration of follow-up:</b> 1.5 years	Newly diagnosed patients with Graves' disease and no GO planned to be treated with antithyroid drugs for 24 months	Establishment of biobank using blood and tear fluid	Demographics, history, clinical/ophthalmological assessments (20) every 6 months. Proteomic, genomic, metabolomics, markers at baseline.	Development of GO over 1.5 years of follow-up and correlation with biomarkers

PICO, patient, intervention, comparator, outcome; GO, Graves' orbitopathy.

### Author Disclosure Statement

No competing financial interests exist.

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