Janice Krushner Memorial Lecture
- London -

2014 Research Update

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I'd like to start by thanking the IGA, and particularly the fundraisers for the IGA, for the research funding which covers about 80 per cent of my salary. So, I hope from what you'll see now you'll be happy with the way some of your patients', members' and public money is being spent!

To give you an overview, (Slide 1) I'm not expecting you to read any of this research output over the last twelve months. That's actually just page one and that's page two, (Slide 2) so over the last twelve months we've had twenty-three peer review publications and you'll see Professor David Crabb's name on many of these because I've been fortunate enough to collaborate with David, as he said, since we were twelve!

But what I'm going to do is just focus on one particular study for most of this presentation and that's the United Kingdom Glaucoma Treatments' Study (UKGTS) which I have presented before, but I'm going to give you an update.

So, this is the first of what we call 'placebo-controlled' trial of medical treatment for glaucoma that has been performed anywhere in the world. We were comparing the effect of latanoprost, or Xalatan, on lowering eye pressure, and the vision preserving benefits of lowering eye pressure, compared to 'no treatment' placebo in the other eye. And last year I presented these results showing the patients on latanoprost had less in the way of progression of visual field loss than patients who were on the placebo. That's good news and enables us to quantify the effect of lowering the pressure in the eye on preserving the field of vision.

This summarises the characteristics of the study (Slide 3) so it was multi-centre, at eleven centres across the UK, double-masked (that means neither the doctors looking after the patients nor the patients themselves knew which treatment they were on) and it was placebo versus active treatment.

We had a little over five hundred patients taking part in the trial which

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Publications for 2013

Slide 1

1. Russell RA, Garway-Heath DF, Crabb DP. New insights into measurement variability in glaucomatous visual fields from computer modelling. PLoS One. 2013 Dec 30;8(12):e83595.
2. Lascaratos G, Garway-Heath DF, Burton R, Bunce C, Xing W, Crabb DP, Russell RA, Shah A; United Kingdom Glaucoma Treatment Study Group. The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, double-masked, placebo-controlled trial: baseline characteristics. Ophthalmology. 2013 Dec;120(12):2540-5.
3. Khawaja AP, Chan MP, Broadway DC, Garway-Heath DF, Luben R, Yip JL, Hayat S, Khaw KT, Foster PJ. Laser scanning tomography in the EPIC-Norfolk Eye Study: principal components and associations. Invest Ophthalmol Vis Sci. 2013 Oct 9;54(10):6638-45.
4. Lamparter J, Russell RA, Zhu H, Asaoka R, Yamashita T, Ho T, Garway-Heath DF. The influence of intersubject variability in ocular anatomical variables on the mapping of retinal locations to the retinal nerve fiber layer and optic nerve head. Invest Ophthalmol Vis Sci. 2013 Sep 9;54(9):6074-82.
5. Ratnarajan G, Newsom W, Vernon SA, Fenerty C, Henson D, Spencer F, Wang Y, Harper R, McNaught A, Collins L, Parker M, Lawrenson J, Hudson R, Khaw PT, Wormald R, Garway-Heath D, Bourne R. The effectiveness of schemes that refine referrals between primary and secondary care--the UK experience with glaucoma referrals: the Health Innovation & Education Cluster (HIEC) Glaucoma Pathways Project. BMJ Open. 2013 Jul 21;3(7).
6. Khawaja AP, Chan MP, Garway-Heath DF, Broadway DC, Luben R, Sherwin JC, Hayat S, Khaw KT, Foster PJ. Associations with retinal nerve fiber layer measures in the EPIC-Norfolk Eye Study. Invest Ophthalmol Vis Sci. 2013 Jul 26;54(7):5028-34.
7. van der Schoot J, Reus NJ, Garway-Heath DF, Saarela V, Anton A, Bron AM, Faschinger C, Holló G, Iester M, Jonas JB, Topouzis F, Zeyen TG, Lemij HG. Accuracy of matching optic discs with visual fields: the European Structure and Function Assessment Trial (ESAFAT). Ophthalmology. 2013 Dec;120(12):2470-5.
8. 8: McNeill A, Roberti G, Lascaratos G, Hughes D, Mehta A, Garway-Heath DF, Schapira AH. Retinal thinning in Gaucher disease patients and carriers: results of a pilot study. Mol Genet Metab. 2013 Jun; 109(2):221-3.
9. Hadwin SE, Redmond T, Garway-Heath DF, Lemij HG, Reus NJ, Ward G, Anderson RS. Assessment of optic disc photographs for glaucoma by UK optometrists: the Moorfields Optic Disc Assessment Study (MODAS). Ophthalmic Physiol Opt. 2013 Sep;33(5):618-24.
10. Khawaja AP, Chan MP, Hayat S, Broadway DC, Luben R, Garway-Heath DF, Sherwin JC, Yip JL, Dalzell N, Wareham NJ, Khaw KT, Foster PJ. The EPIC-Norfolk Eye Study: rationale, methods and a cross-sectional analysis of visual impairment in a population-based cohort. BMJ Open. 2013 Mar 19;3(3).
11. Davey PG, Elsheikh A, Garway-Heath DF. Clinical evaluation of multiparameter correction equations for Goldmann applanation tonometry. Eye (Lond). 2013 May;27(5):621-9.
12. Redmond T, Anderson RS, Russell RA, Garway-Heath DF. Relating retinal nerve fiber layer thickness and functional estimates of ganglion cell sampling density in healthy eyes and in early glaucoma. Invest Ophthalmol Vis Sci. 2013 Mar 1;54(3):2153-62.
13. Crabb DP, Smith ND, Glen FC, Burton R, Garway-Heath DF. How does glaucoma look?: patient perception of visual field loss. Ophthalmology. 2013 Jun;120(6):1120-6.

Publications for 2013

Slide 2

14. Ratnarajan G, Newsom W, French K, Kean J, Chang L, Parker M, Garway-Heath DF, Bourne RR. The impact of glaucoma referral refinement criteria on referral to, and first-visit discharge rates from, the hospital eye service: the Health Innovation & Education Cluster (HIEC) Glaucoma Pathways project. Ophthalmic Physiol Opt. 2013 Mar;33(2):183-9.
15. Redmond T, Zlatkova MB, Vassilev A, Garway-Heath DF, Anderson RS. Changes in Ricco's area with background luminance in the S-cone pathway. Optom Vis Sci. 2013 Jan;90(1):66-74.
16. Asaoka R, Russell RA, Malik R, Garway-Heath DF, Crabb DP. Five-year forecasts of the Visual Field Index (VFI) with binocular and monocular visual fields. Graefes Arch Clin Exp Ophthalmol. 2013 May;251(5): 1335-41.
17. Lascaratos G, Shah A, Garway-Heath DF. The genetics of pigment dispersion syndrome and pigmentary glaucoma. Surv Ophthalmol. 2013 Mar-Apr;58(2):164-75.
18. Day AC, Garway-Heath DF, Broadway DC, Jiang Y, Hayat S, Dalzell N, Khaw KT, Foster PJ. Spectral domain optical coherence tomography imaging of the aqueous outflow structures in normal participants of the EPIC-Norfolk Eye Study. Br J Ophthalmol. 2013 Feb;97(2):189-95.
19. Ratnarajan G, Newsom W, French K, Kean J, Chang L, Parker M, Garway-Heath DF, Bourne RR. The effect of changes in referral behaviour following NICE guideline publication on agreement of examination findings between professionals in an established glaucoma referral refinement pathway: the Health Innovation & Education Cluster (HIEC) Glaucoma Pathways project. Br J Ophthalmol. 2013 Feb;97(2):210-4.
20. Garway-Heath DF, Lascaratos G, Bunce C, Crabb DP, Russell RA, Shah A; United Kingdom Glaucoma Treatment Study Investigators. The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, placebo-controlled clinical trial: design and methodology. Ophthalmology. 2013 Jan;120(1):68-76.
21. Wang YX, O'Leary N, Strouthidis NG, White ET, Ho TA, Garway-Heath DF. Comparison of neuroretinal rim area measurements made by the Heidelberg Retina Tomograph I and the Heidelberg Retina Tomograph II. J Glaucoma. 2013 Oct-Nov;22(8):652-8.
22. Asaoka R, Russell RA, Crabb DP, Garway-Heath DF. Visualizing the hill of vision in 3D using the free programming language 'R'. Graefes Arch Clin Exp Ophthalmol. 2013 Jan;251(1):391-2.
23. Elsheikh A, Gunvant P, Jones SW, Pye D, Garway-Heath D. Correction factors for Goldmann Tonometry. J Glaucoma. 2013 Feb;22(2):156-63.

lasted two years for each subject. One of the major reasons for doing the trial was to assess whether or not we could improve the power of the study by looking at the velocity of progression in the visual field, and I'll describe what I mean by that in a moment, and also by combining images of the nerve with the visual field testing. What's meant by study power is basically the number of subjects needed for a study and the duration of a study. We're aiming to shorten the duration of studies and also enable the studies to be performed with fewer patients to make them more cost-effective.

Conventionally, visual field progression is assessed in the software of the visual field machine by comparing the most recent test with the baseline (first) tests. But what we wanted to do was identify whether or not we could measure the speed of change in the visual field and use that as an outcome that may be more sensitive than using the conventional approach. As I've mentioned, we also wanted to assess whether or not measuring 'structure' through imaging of the optic nerve would enable us to tell the difference between the treatment arms. We were also interested in looking at the risk factors for progression and, of course, we know the most important of these risk factors is intraocular pressure. As there are various new devices around for measuring pressure, we wanted to establish if one of these devices was better than the others. (Slide 4) This is the result of looking at the velocity of progression as an outcome for this clinical trial. What we can see here is the sixth-month time point and we're asking the question "can we tell the difference between the treated group and the placebo group?" This P value is the sensitivity; it tells us whether or not it is statistically significant and usually we take the 5 per cent level for statistical significance. If we look at our new technique, developed by one of Professor David Crabb's and my post doctorate students Haogang Zhu, this technique, after six months of observation, was able to tell the difference between the treatment groups and that difference was more significant at longer observation periods. What this means is that we can do clinical trials now with observation periods of only one year, which is a big advance on previous studies.

In fact what I've done here (Slide 5) is what we call 'power calculations', to look to see how many patients we would need for a one-year clinical trial using our new methods. And about two hundred patients in each treatment arm are required for a years' study where we think the treatment effect would be a thirty per cent reduction in the speed of progression of the visual field. This is a hugely reduced number than previous clinical trials in glaucoma.

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UKGTS

UK Glaucoma Treatment Trial

- multicentre, double masked, randomized, placebo-controlled treatment trial for manifest glaucoma
- 516 newly diagnosed, previously untreated subjects
- 2-year (per subject) duration
- designed to assess whether study power can be improved by looking at
  - rates (velocity) of progression
  - combining imaging of the optic nerve and visual field testing

Slide 3

Velocity of progression

N = 437		ANSWERS (mean 10 fastest locations)	MD
6 months	Placebo	-3.92 (3.10)	0.03 (-2.09, 1.72)
	Treatment	-3.01 (2.59)	0.57 (-1.59, 2.16)
	p	0.03%	17%

Slide 4

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What this means is that "yes", the rate of visual field change does provide a sensitive outcome but the duration of a trial can be greatly reduced and new treatments can be brought to patients more quickly. It also means, because of the shorter duration, it's more affordable for pharmaceutical companies to investigate new potential treatments and it makes this more likely because it's less expensive to try a variety of treatments and find new ones that will be advantageous to patients. That's a big 'tick' for the result of the speed of progression outcome for the UKGTS.

The next question was around imaging, because there's been a lot of hope in the past that imaging devices, which can image the optic nerve head or the nerve fibre layer around the optic nerve head, would be more sensitive even than visual field testing. There's actually very little evidence in the literature at the moment to demonstrate that imaging is useful or, if it is useful, in which clinical circumstances. So we set out to see whether or not imaging could tell the difference between the treatment groups in the UKGTS. We had three different imaging devices that we call 'HRT' (that's the Heidelberg Retina Tomograph, rather than hormone replacement therapy which you might be thinking!), 'OCT' (optical coherence tomography) and the 'GDx' (which is short for glaucoma diagnosis) nerve fibre analyser. We didn't have all the instruments at all the study sites, so this is the number of patients that were imaged with each of the devices (Slide 6).

(Slide 7) This is for the Heidelberg Retina Tomograph and it is comparing the placebo and the treated groups and this P value is less than the five per cent level, that tells us the HRT is able, with high significance, to be able to distinguish the treatment groups. Imaging is not doing quite as well as visual fields, but we know that the structure measurements may support the visual field measurements we take, so the hope is that by combining the imaging with the visual field testing, we will be able to add more power still to our clinical trials.

These are the OCT results; (Slide 8) we've achieved the four per cent significance level here, so the OCT can distinguish between the treatment groups. It was less good news for the instrument called the GDx. (Slide 9) There was no statistical difference but at least this is telling us at least two of the devices are able to identify treatment effects and combining imaging with visual field testing may enable the duration of clinical trials to be reduced even further, so this is definite progress so far as imaging is concerned.

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Sample size calculations

Slide 5

	ANSWERS			PLR		
Rate reduction	Slope (UKGTS latanoprost arm): mean (sd)	Target slope with neuro-protective treatment	Sample size (per arm)	Slope (UKGTS latanoprost arm): mean (sd)	Target slope with neuro-protective treatment	Sample size (per arm)
10%	-2.47 (2.25)	-2.22 (2.25)	1703	-6.58 (6.37)	-5.93 (6.37)	2019
20%	-2.47 (2.25)	-1.98 (2.25)	444	-6.58 (6.37)	-5.27 (6.37)	497
30%	-2.47 (2.25)	-1.73 (2.25)	195	-6.58 (6.37)	-4.61 (6.37)	220

Modelling for a trial of neuroprotection
Assumptions:
Patients on latanoprost
Observation period 12 months
Power 90%
P 5%

Inclusion criteria

Slide 6

1. more than 6 months follow up
2. Image quality (OCT: SS≥7, HRT:SD≤40, GDx: Quality≥8 TSS≥70)
3. HFA reliability (FP<15%)
4. worse MD eye

Number of eyes fulfilling the above conditions

HRT
407 eyes of 407 subjects

OCT
274 eyes of 274 subjects

GDx
252 eyes of 252 subjects

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I'm going to talk about risk factors now. As I mentioned, we are particularly interested in the intraocular pressure measurements; you have those measurements every time you go to the clinic and there are new instruments available. One is called the 'Dynamic Contour Tonometer' and another is called the 'Ocular Response Analyser'. We wanted to see whether or not the pressure measurements with these devices was more or less closely associated with progression (the change in the visual field over time) because we want a pressure testing instrument that predicts progression in the visual field. So we compared those to the standard blue light Goldmann Applanation Tonometer. We had this number of subjects that had pressure measurements with all these devices and we also know the rate of change in the field of vision in these patients. So what we're doing is comparing the pressure measurements, with each of these, with the rate of visual field change. And these are the results we get: (Slide 10).

This 'r' value tells us how closely the pressure measurement is related to the rate of visual field change; the higher the number the better. None of the numbers are particularly high, which means the pressure on its own only tells part of the story, but the highest number is for the Ocular Response Analyser, the air puff tonometer.

This statistical technique, the Akaike Information Criterion, tells us how likely it is that one of these measurements is better than another. If we look at the Akaike Weight, this is the best way of looking at the results. There's ninety-two per cent probability the Ocular Response Analyser is the best and only a six per cent chance that the standard instrument, the Goldmann Tonometer, is the best.

This is telling us, going forward, we're going to be better off in identifying patients at risk of further visual field loss by using the Ocular Response Analyser. Having said that, it's only a small gain.

Our conclusion is, first of all, that the rate of progression is relatively poorly predicted by eye pressure on its own. Therefore there are other factors we need to look for and the best measurements are predicted by the Ocular Response Analyser.

To finish, I'm just going to tell you about some new grants that I've been successful in gaining with my colleagues. The reason I'm showing this is because it gives you an idea of how your investment in the IGA Chair pays off and how much more money I am able to bring into glaucoma research through your investment.

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HRT result (n = 407)

(p value: t-test)

Slide 7

Characteristics of eyes **at Baseline**

	Placebo (n=197eyes)	Latanoprost (n=210eyes)	p value
age	65.3	64.4	0.389
MD	-4.13	-4.03	0.764
rim area	1.05	1.01	0.238
disc area	2.03	1.99	0.334
follow-up months	19.1	20.5	< 0.01
visits	8.7	9.1	0.103

Difference in changes between placebo and latanoprost

	placebo	latanoprost	p value
rim area slope	-0.021	-0.013	0.016
MD slope	-0.38	0.01	< 0.01

Rim area rate reduction = 38%

Stratus OCT result (n = 274)

(p value: t-test)

Slide 8

Characteristics of eyes **at Baseline**

	Placebo (n=134eyes)	Latanoprost (n=140eyes)	p value
age	65.1	64.6	0.654
MD	-4.28	-4.10	0.652
average NFLT	1.05	1.02	0.294
follow-up months	19.4	20.6	0.082
visits	8.9	9.1	0.480

Difference in changes between placebo and latanoprost

	placebo	latanoprost	p value
NFLT slope	-2.166	-1.152	0.039
MD slope	-0.44	0.05	< 0.01

RNFL rate reduction = 47%

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This is the first grant and David Crabb has already alluded to this. It is a grant to develop a new visual field test that is more patient-friendly. It's funded by the National Institute for Health Research (NIHR) and all their research funding is very patient-focussed. They like to see patients intimately involved in generating the research ideas and in running the research studies themselves. In fact, one of my patients is an investigator herself in this study and I know Sheila Page, an IGA Trustee, is also an applicant on one of the NIHR studies that David Crabb performed. In our objectives for this project, we say that making the visual field test more patient-friendly because the perimeter results are variable, requiring many tests over a long period of time to assess the extent of vision loss, are inconvenient to patients and patients don't enjoy the experience. So there are several aspects of this research where we're looking to improve the experience for patients.

One, for instance, is that the current visual field test machine will test regions of the visual field whether or not a patient can see in that region. When we have prior test data from a patient, we know which areas of the field the patient is not seeing however, the current machines goes on testing it. So, patients find themselves sitting in front of the machine waiting for something to happen, which must be frustrating. Also it's a difficult task; patients have to identify targets that are on the threshold of brightness that can be seen. We're going to take a different approach where we'll be closer to the brightness that patients can see and we're going to change the size of the target, which we think will be an easier task to perform. The research grant is £750,000. If we add that to a grant I received last year that's over £1 million of research funding I've been able to bring into glaucoma research over the last two years.

Another study, which is a PhD studentship, funded by Fight for Sight on this occasion, is looking at susceptibility factors additional to pressure. I explained the pressure is only part of the story, there are other things that make people susceptible to progression and we believe mitochondria is one of them. Mitochondria is the little power packets that power cells, inside every cell of your body, and we believe that if these mitochondria are not producing enough power that makes you more susceptible to developing glaucoma. So this is a new PhD programme under way now.

I've also been a co-applicant on other research grant applications bringing in a total of between £3 million and £4 million. This is headed by Anthony King in Nottingham and is a grant for nearly

GDx result (n = 252)

(p value: t-test)

Characteristics of eyes **at Baseline**

	Placebo (n=119eyes)	Latanoprost (n=133eyes)	p value
age	63.5	63.0	0.757
MD	-3.74	-3.69	0.877
TSNIT average	41.7	42.9	0.152
follow-up months	19.6	21.2	0.013
visits	9.0	9.4	0.247

Difference in changes between placebo and latanoprost

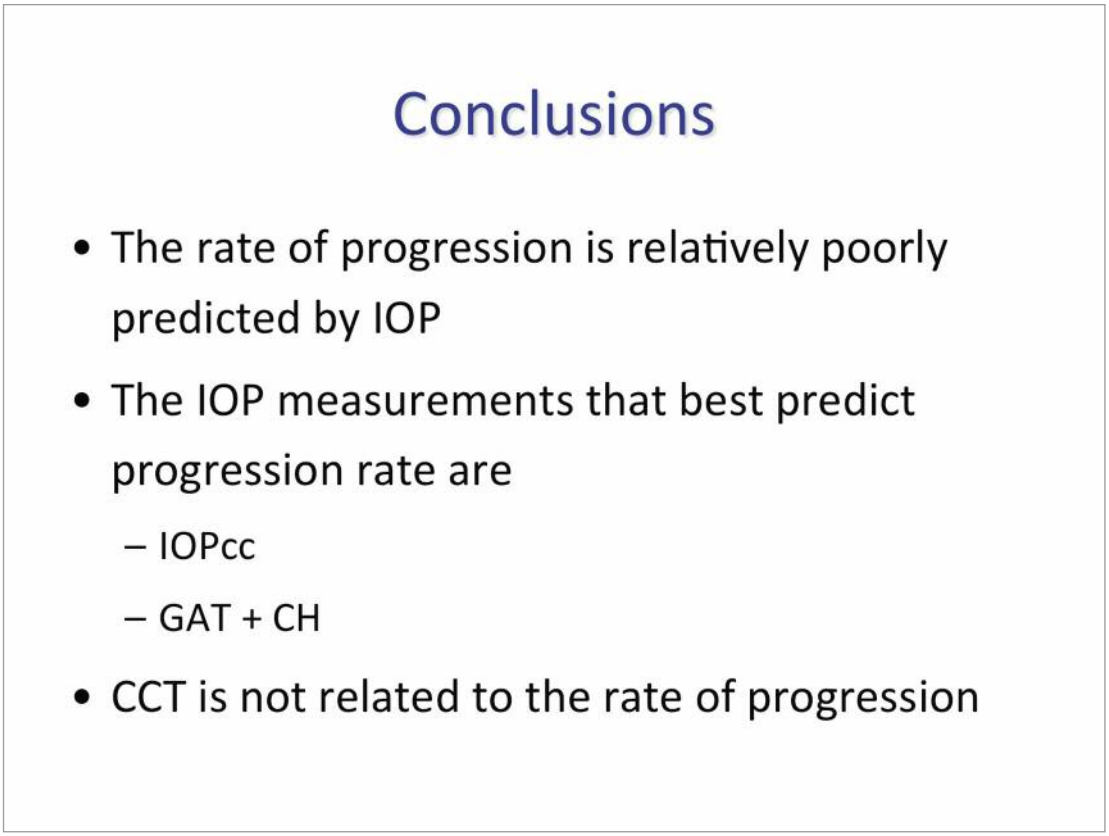
	placebo	latanoprost	p value
TSNIT slope	-0.800	-0.871	0.717
MD slope	-0.35	0.07	< 0.01

Slide 9

Results

N = 342	r	AIC	Akaike weight
GAT	0.25	1337	0.06
DCT	0.20	1346	0.00
ORA IOPg	0.24	1339	0.02
ORA IOPcc	0.28	1331	0.92
CCT	0.02	1361	0.00

Slide 10



Slide 11

£2 million. It is asking the question whether or not early surgery, compared to medicine, is advantageous for patients that present with advanced glaucoma at the outset. Because that's something we don't know at the moment. We believe early surgery may be advantageous, but we need to show it. Significantly, the feasibility work to do this study was funded by the IGA. So it was the IGA's funding that enabled this project to go for NIHR funding for this large sum of money. Once again it's thanks to the IGA for their wise investment in research to pump prime early work and stimulate larger research projects down the line. Thank you for your attention.

Questions and Answers

Q. Hello. Is any research being done on the blood supply to the eye? I've got advanced stage glaucoma and optic nerve atrophy, which is something to do with the blood supply.

A. The answer is "yes". There's a 'but' though, which is that research is quite difficult because there's a sort of chicken and egg question, "is blood supply poor in an eye with glaucoma because the eye doesn't need so much blood because some of the nerves cells have died, or, have the nerve cells died because blood supply is poor?" In its most simplest form, we know that

blood pressure is important and there's a lot of data published in the literature at the moment to suggest that people who are over-treated for high blood pressure are more at risk of developing glaucoma and more at risk of their glaucoma worsening. So we're beginning to understand the blood pressure aspect. There are researchers developing new imaging devices to measure blood flow and I'm optimistic that, in the not too distant future, we'll have devices that are able to measure, not just the flow of blood inside the eye, but the size of the blood vessels and the amount of oxygen in the blood, so we can get a complete picture of the supply of oxygen to the tissues in the eye. In summary the answer is "yes", but there aren't any easy answers to give you at the moment.

Q. It's all very well shortening the periods for the tests and making it cheaper for pharmaceutical companies, but how do we know the tests are therefore rigorous enough for us?

A. Well that's a very good point and I have another grant which I mentioned last year, again with David Crabb. This is to ensure the techniques we're developing for clinical trials will also be applicable in clinical practice and the post-doctorate research fellow I mentioned has already developed some software for combining the structural measurements and the visual field measurements for use in the clinic. So you're absolutely right, we need them for clinical practice; in the not too distant future, when we have the electronic records that we need in the clinics up and running, we'll be able to use all this data in the clinic.

Q. I've read some articles about stem cells and optic nerves. Is there any research? They tell me that's my only hope now to stop blindness.

A. I would hope that in your case it's not a question of needing to stop blindness, all things being equal it's usually possible to slow the rate of disease progression so people maintain most of their vision for life. Our hope for stem cell therapy is that it will be able to replace lost vision; to actually give you back vision that you've already lost. Now again, in glaucoma, it's a particularly difficult task because stem cells need to be turned into nerve cells, the nerve cells need to connect up with all the other cells in the retina and then connect to the brain. So there are a lot of hurdles to overcome, but "yes" there are people working on this. Professor Astrid Lim of the Institute of Ophthalmology is actually looking at the use of stem cells for glaucoma. So there are people investigating but the time scale is difficult to predict.

Q. Hi. Sounds like a silly question but how does this tie in internationally with the stuff that you're doing in this country with everybody else and is

Q&A

everybody else as good as you?

A. The answer is that we collaborate a lot. With the visual field testing, we often refer to ourselves as the "visual field anorak club!" because we're all fascinated by visual field testing and we all know each other very well and there are pockets of research groups around the world and we all talk to each other.

But what would be very nice to see is some of the innovations that we've been bringing to the clinic in the UK being developed for smartphones for use in Africa, which was a particular goal with some of the research we've been doing, that I presented previously.

There's a very high chance the Moorfields Motion Detection Test, (M.D.T) which is an oscillating line to check the field of vision, could go on the smartphone and be used to test vision in parts of the world that don't have access to the more sophisticated devices we have here.

Keith Barton
Thank you very much Ted and ladies and gentlemen for coming today and for staying to the bitter end. I am especially encouraged by the fact the numbers are higher at the AGM this year. People aren't losing interest in the IGA; hopefully they're gaining interest and you can see from what's been going on this afternoon the IGA's involvement in research and innovation is actually quite high despite our very small size in comparison to some other charities.

I've a patient who raises money for the RNLI and I asked her one day how much money she raised and I can't remember if it was £29,000 annually or £129,000!

So we're very small in comparison but it's encouraging the IGA does have quite a high profile for its small endeavours and it's thanks to the members and the donors who keep this going.

Thank you very much for coming and safe journey home tonight. We would be delighted to see you again next year.