Refractory Asthma Stratification Programme

Oct 2016

Breathe Deep: Issue 3

Welcome to the third issue of the Refractory Asthma Stratification Programme (RASP-UK) newsletter!

Inside:

Welcome to the latest Refractory Asthma Stratification Programme - UK Newsletter

by Gabrielle Gainsborough, Consortium Manager

Welcome to the latest Refractory Asthma Stratification Programme (RASP-UK) newsletter. We are almost 1 year into the programme and have already seen great progress since we signed the consortium agreement October 2015.

Recruitment into Work-strand 1 (Adherence, INCA-SUN and Biomarker Stratification Study) and Work-strand 3 (SoMOSA) continues to be our main focus. However since the last newsletter we have had Research Ethics Committee and Health Research Authority approval for the Work-strand 2 Bronchoscopy study with first Trust approval at Leicester.

In this edition we'll share updates on the programme as well as some more in-depth information on selected work-strands. We would be delighted to hear from you if you would like to share any relevant news with the consortium through this newsletter or if you have any suggestions or comments on the RASP-UK programme. You may even like to contribute a short article. So please get in touch with me, Gabrielle Gainsborough, at Niche Science & Technology Ltd. gabrielle.gainsborough@niche.org.uk

In this issue we cover…

- RASP-UK First Trial Steering Committee Meeting
- Work-strand 2 Bronchoscopy study: an overview
- A fond farewell to Courtney Coleman
- Patient involvement, engagement, participation and experience...what is it and why is it important?
- Update on work-strand progress
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A Fond Farewell

Courtney Coleman, who has supported RASP-UK over the past 2 years and has been responsible for setting up and managing our Patient Input Platform, has sadly left Asthma UK. We thank Courtney for all her help with the programme, and wish her well in her new role. Nile Amos, will take over from Courtney in supporting RASP-UK.

RASP-UK First Trial Steering Committee Meeting

by Gabrielle Gainsborough, Consortium Manager

On 7 September 2016, the first meeting of the RASP-UK Trial Steering Committee (TSC) was held at Asthma UK's offices in London. The RASP-UK TSC monitor safety in Work-strands 1,2 and 3. The committee had no safety concerns. They were very interested in the background to the study and identified no safety issues thus far. They congratulated the team on their progress to date and agreed that the next review should take place in March 2017.

Work-strand 2 Bronchoscopy study: an overview

by Professor Peter Bradding , Work-Strand 2 Lead

Ten percent of patients with asthma have treatment-resistant (severe) disease. Until recently asthma was considered as a single disease caused by Th2-driven eosinophilic airway inflammation, and a “one size fits all” approach to therapy and drug development has dominated the field. As a result, development of effective new treatments has met with limited success.

Professor Peter Bradding

Statistical analyses have identified up to four clinical phenotypes of severe asthma, characterised by the presence or absence of eosinophilia. Distinct molecular pathways (endotypes) are also evident in asthma airways, but how these relate to the clinical expression (phenotype) is unclear. For example, only 50% of patients with asthma may have a significant Th2/eosinophilic profile of airway inflammation. We do not understand the mechanisms driving Th2-low asthma, although a proportion of these patients have evidence of IL-17-dependent gene transcription. Stratifying severe asthma based on the underlying molecular pathways is therefore critical for the identification and appropriate targeting of novel therapies.

Work to-date examining the immunopathology in patients with severe asthma has been undertaken in patients using high doses of inhaled/oral corticosteroids. Corticosteroids alter gene and protein expression, raising uncertainty as to whether novel observations uncovered in asthmatic airways compared to non-asthmatic airways are due to the disease or the treatment. We believe that by studying patients who have their dose of corticosteroids optimised, we have a better chance of uncovering the mechanisms driving non Th2 asthma.
In workstrand 1 of RASP, we are undertaking a biomarker-driven study using a composite score derived from blood eosinophils, exhaled FeNO and serum periostin as a surrogate of Th2-driven disease. This biomarker-driven treatment optimisation approach aims to uncover 3 groups – a true corticosteroid “resistant” Th2-high group (biomarker positive despite high dose inhaled corticosteroids), a corticosteroid-sensitive group who have a controlled Th2 component that may resurface on steroid down-titration (initially biomarker-low), and a Th2-low group who remain biomarker low on down-titration. Our aim therefore is to undertake bronchoscopy in a subset of patients who have undergone treatment optimisation, to uncover mechanisms driving Th2-low asthma.

RASP Refractory Asthma Stratification Programme

Work-strand 2: Overview (continued)

by Professor Peter Bradding

Patient recruitment and stratification is summarised in the flow diagram in figure 1. The following patients will be invited to participate:

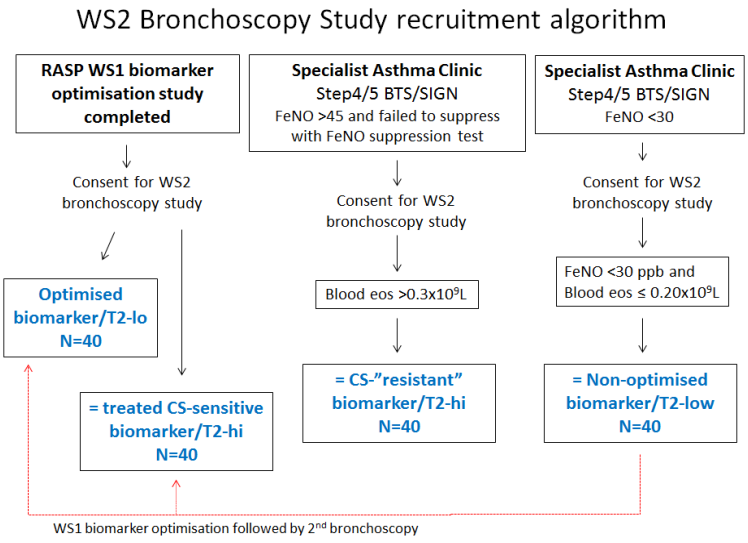
i. Patients identified in clinic with FeNO <30 ppb. Those who at screening demonstrate FeNO <30 ppb and blood eosinophil count ≤0.20 x10^9/L will be considered to be non-optimised biomarker-low patients (Th2-low) and will proceed to bronchoscopy. If they then take part in the RASP workstrand 1 corticosteroid optimisation study, they will then be invited to undergo repeat bronchoscopy at the end of this.

ii. Patients identified in clinic with FeNO >45 ppb who have failed to suppress their FeNO during FeNO suppression testing. These patients are considered adherent to inhaled corticosteroids. Those who at screening also demonstrate blood eosinophils of >0.3x10^9/L represent a corticosteroid-resistant biomarker/Th2-high group.

iii. Optimised corticosteroid-sensitive biomarker/Th2-high (on ICS down titration) and optimised biomarker/Th2-low patients will be identified from RASP WS1.

We are aiming for 40 patients in each group (160 total). The primary endpoint is the identification of molecular pathways, identified through gene expression analysis of airway biopsy tissue, related to distinct clinical phenotypes of severe asthma. Secondary/Exploratory Efficacy Endpoints are:

- Airway cellularity and structure in relation to clinical phenotype of severe asthma
- Airway protein expression in relation to clinical phenotype of severe asthma
- Peripheral blood gene expression in relation to clinical phenotype of severe asthma
- The airway microbiome in relation to molecular pathways and clinical phenotype of severe asthma
- Differentiation of pathways, biomarkers, and heterogeneity between gene expression and pathophysiology in severe asthma



Refractory Asthma Stratification Programme

Patient involvement, engagement, participation, input and experience...

...what is it and why is it important?

By Kathy Hetherington, Researcher, QUB and Jenny Negus, RASP-UK Patient Input Platform

In the last RASP-UK newsletter Courtney Coleman from Asthma UK outlined the role of the RASP-UK Patient Input Platform (PIP), how it was formed and how is has contributed to the project so far. As a member of the PIP and a research co-ordinator, we wanted to give our views of what being involved means to us.

The Patient – Jenny

I am a 40 year old brittle asthmatic who is on first name terms with most of the paramedic and ED staff in South West England and know the personal and social lives of many of the respiratory ward staff at the local hospital. I retired from the nursing profession in 2006 as I was more patient and less nurse! I am currently involved with many projects through Asthma UK and other organisations. I am studying for a Masters Degree in Health Communication. It is therefore a 'many hatted' (not always mad hatted!) approach that I bring to the PIP.

Being a patient can be a very dis-empowered, demoralising and confusing role to have. Suddenly you stop being you and become your condition. You are unsure how the system works and there is masses of technical speak flowing around you. To top it off there are doctors who look young enough to still be at school in charge of your care and medications!

We are the patients that researchers want and **need** to engage within their projects.

This is where PIP comes in. On one hand there are doctors, researchers and scientists who aim to improve the lives of the patients but need some help and input from "real patients". On the other hand are the many patients who would love to help but don't know how. We provide the bridge over the inevitable gap between the two factions.

Patient involvement...

… and why is it important? (continued)

The Researcher – Kathy

I am a 23 year old student just starting the final year of my PhD. As a young researcher I feel very privileged to have been brought into RASP-UK by Professor Heaney and given the opportunity to be able to work with a wide range of fantastic clinicians, patients and co-ordinators. My PhD is focused on using novel remote technology to monitor corticosteroid responsivity and adherence in asthma and I have spent the past year coordinating the 'Non-Adherence' arm in RASP-UK. Working with many of the investigators, clinics and research staff involved in this project has emphasised the wealth and variety of knowledge available, to which I was keen to add a patient's perspective.

The project that I am collaborating with the PIP on is a qualitative piece related to the 'Non-Adherence' arm. The project is hoping to identify features within difficult asthmatics' behaviour that is changed or modified following FeNO Suppression testing (inhaled steroid responsiveness testing) and to explore patient views and opinions surrounding inhalers, treatment monitoring and medication adherence. I was able to call upon the PIP to inform the schedule of questions, consent form, patient information sheet and the protocol and this has been invaluable

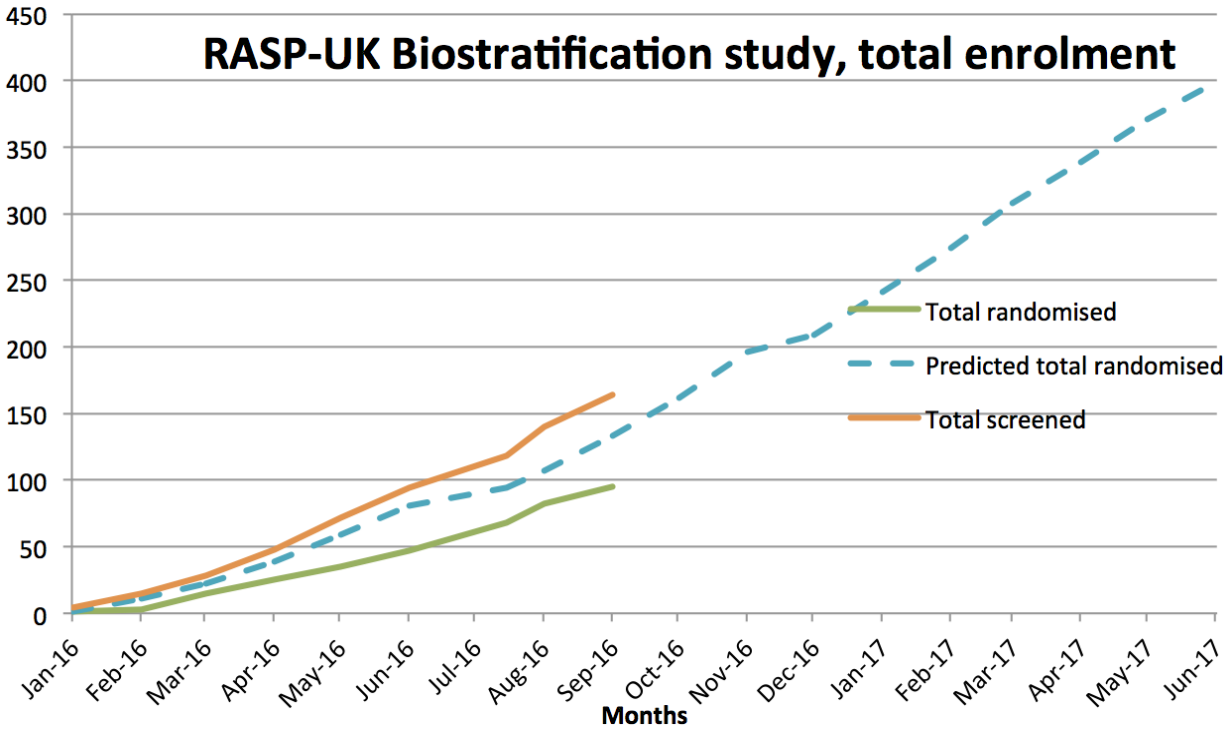
By asking the PIP to look at protocols, questionnaires, patient information sheets etc, researchers are acknowledging that what seems simple to them might be confusing, frightening or even unacceptable to patients. The PIP can look at them through the eyes of a patient, but with extra experience and knowledge gained through our role, and consequently work with the researchers to adapt the information or tools to enable them to be used effectively. The common goal we all have is for successful, informative and innovative research to take place and the advancement of knowledge and understanding. Encouraging patient involvement and participation in research, through clear, concise and accessible information is key to future research success.

If you'd like to know more about the PIP or would like their input, please contact Nile Amos at Asthma UK: namos@asthma.org.uk

Work-strand 1 Biostratification Study update

By Dr Avril Horn
Work-strand 1 Project Manager

Thanks to everyone's efforts during September, we maintained the screening rate and now have 164 patients screened. The randomisation rate was lower than anticipated, with 13 patients randomised. We now have a total of 95 patients randomised.



Review of screen failures in RASP biostratification study

We have been recruiting in to the biostratification study since late December 2015 and our first patient was randomised on 8 January 2016. We now have 95 patients randomised. When the study started, we had anticipated that with adequate pre-screening we would achieve a screen failure rate of approximately 20%, and that four out of five patients screened would proceed to randomisation. We have since found that our screen failure rate is 40%, and that we currently have 54 patients who have been screened but not randomised.

Work-strand 1: Update (continued)

The most common reason screen failure is FeNO >45 ppb (n-19) – please try and identify these patients before considering them for the study by careful pre-screening assessment in clinic – including FeNO measurement – these patients can still proceed to inclusion in the adherence assessment part of the programme.

It is important to recognise that some of the patients who screen fail are eligible for rescreening, (patients can be rescreened up to three times) particularly those who have failed screening for the following reasons:

- No documented reversibility of FEV_1 = 11
- Recent exacerbation = 9

Patients without a documented reversibility of FEV_1 can be enrolled in to the study on the basis of **variability** of 12% in FEV_1 in the past 24 months. If there are two documented measurements of FEV_1 which are technically satisfactory and vary by 12% or more during the past 24 months, then the patient is eligible for enrolment.

Depending on the patient's work and family commitments, these patients can also be asked to withhold their morning dose of bronchodilator, with FEV_1 then being measured before and after bronchodilator use. In addition, these patients can have methacholine testing when bronchodilators are withheld for the previous 24 – 48 hours (depending on their specific prescribed LABA or LAMA treatment) to show evidence of bronchial hyper-responsiveness.

Patients who have had an exacerbation of their condition can be rescreened for entry four weeks after they have recovered from the exacerbation.

Please can we ask you to review the patients at your centre who have failed screening to see if there is any opportunity for these patients to be rescreened for entry.

Work-strand 1

A prospective randomised multicentre study to optimise management of symptomatically uncontrolled asthma patients (INCA-Sun)

By Professor Richard Costello and Lorna Lombard, Royal College of Surgeons in Ireland

The INCA-Sun study is now open in four centres in Ireland. To date, 38 patients have been enrolled into the study, six of which have already completed all of the study visits.

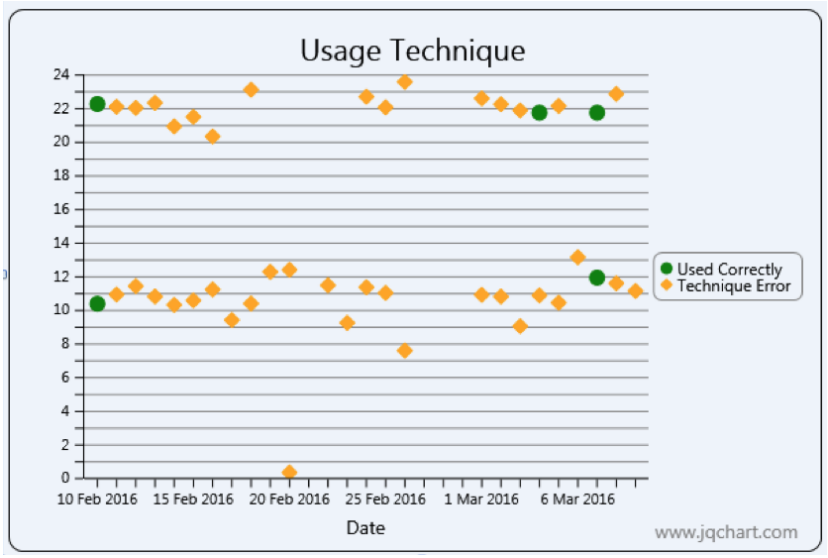
The first graph below was generated by the INCA technology. This graph shows the habit of use and inhaler technique of one of the patients during her first month in the study. This patient was given full inhaler education prior to this month. The yellow dots on the graph represent when she used her inhaler incorrectly and the green dots represent when she used her inhaler correctly. After the first month, this patient was shown this graph and she was educated based on her errors detected by INCA technology. The error in this patient's case was 'no inhalation detected' which meant she was not inhaling her medication.

INCA
Inhaler Compliance Assessment

RCSI

HRB
Health Research Board

INCA-Sun update (continued)

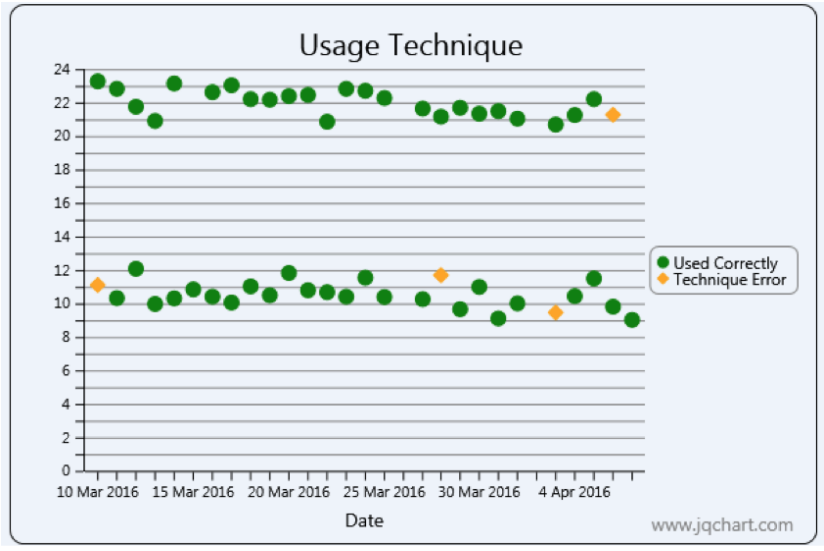


INCA

Inhaler Compliance Assessment

GlaxoSmithKline

The second graph was generated a month after the patient had received the INCA technology assisted education. As can be seen from this graph the green dots represent that the patient has taken her inhaler correctly the majority of the time which is in complete contrast to the previous month. By the end of the study this patient had reduced her Seretide dose from 500/50mcg to 250/50mcg, she did not require oral steroids and only used Ventolin occasionally compared to daily use. Her asthma is now controlled.

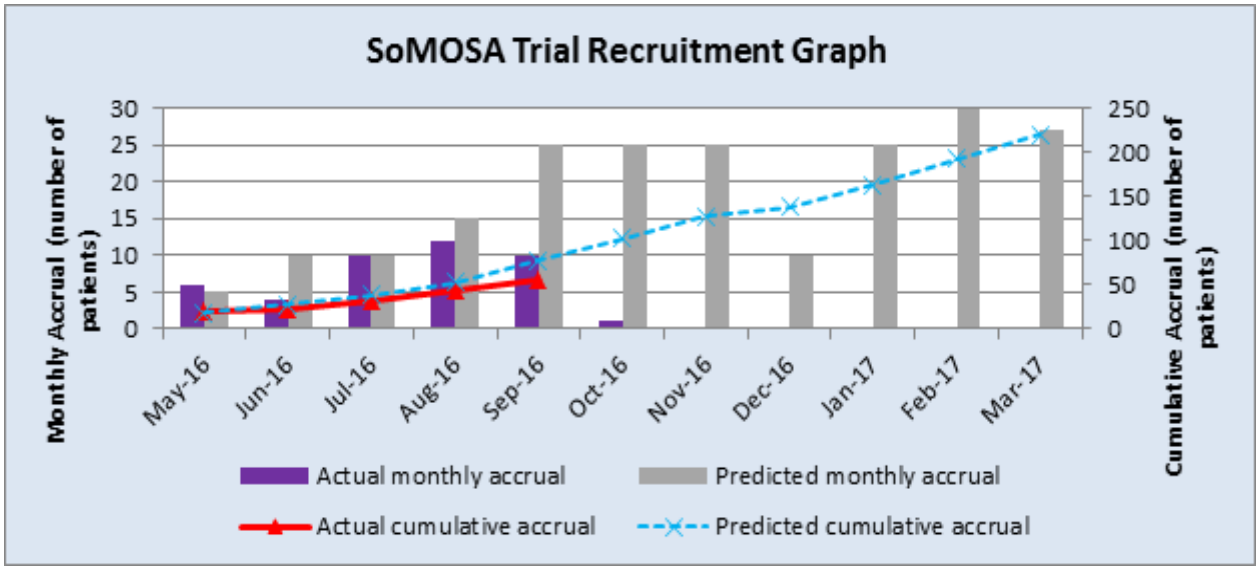


For the latest updates and news on the INCA technology you can follow us on: twitter@INCA_team

Work-strand 3

SoMOSA Update

Recruitment into the study continues to be slower than anticipated. We currently have 61 randomised patients in the study. The Work-strand 3 team would like to thank all of the sites for their support and commitment to date.



Save the date! We are planning the RASP-UK 2016 General Assembly Meeting - please put Tuesday 6th December 2016 in your diaries!

RASP UK Events

- MRC Stratified medicine Monitoring Group Meeting – 18th November

Website

The RASP-UK website holds copies of all relevant study documents through the secure login portal at: http://www.rasp.org.uk/.

If you would like to add any documents to the website or if you have and questions or comments on the website, please contact Gabrielle at Niche Science & Technology Ltd (gabrielle.gainsborough@niche.org.uk)

Newsletters

Please let us know if you would like to share any news with the RASP-UK consortium. Your suggestions or comments on the RASP-UK programme are always welcome! Simply contact Gabrielle at Niche.

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