Statistical Analysis Plan

Eczema Care Online (ECO)

Trial name:	Eczema Care Online (ECO)
Trial registration number:	https://doi.org/10.1186/ISRCTN79282252
Protocol title and version number:	
SAP version number:	1
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To be approved and reviewed by:

	Name	Signature	Date
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1. Purpose of the SAP

The Statistical Analysis Plan provides a comprehensive and detailed description of the methods and presentation of data analyses proposed for the "Eczema Care Online (ECO)" trials.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. Study Design

2.0 Trial background and rationale (short synopsis from trial registration)

Eczema is a common skin disorder causing itchy skin and dryness. Eczema leads to poor quality of life (sore or bleeding skin, itching and poor sleep). Most people with eczema benefit from two treatments: (1) moisturisers (emollients) for dry skin, which need to be applied daily; and (2) topical corticosteroids for inflamed skin and eczema flares. Commonly, if eczema is not well-controlled it is because treatments are not used appropriately. There are many reasons why people may find it difficult to use eczema treatments: they can be time-consuming to apply; treatments may sting when first applied to inflamed skin; there are concerns about the safety of some treatments; and because people often receive conflicting or insufficient advice about how and when to use treatments.

The trialists have developed two online toolkits to support self-management of eczema: (1) for young people with eczema (aged 13-25 years); and (2) for parents/carers of children with eczema (aged 0-12 years). Toolkits cover a range of topics relevant to people with eczema.

2.1. Trial aims and objectives

The purpose of these trials is to determine the clinical and cost-effectiveness of online interventions for eczema: trial-YP for young people aged 13-25 with eczema (intervention-YP) and trial-PC for parents/carers of children aged 0-12 with eczema (intervention-PC).

2.2. Trial design and configuration

The two ECO trials are pragmatic randomised open-label multicentre superiority trials, each with two parallel groups.

2.3. Trial centres

The ECO study will recruit participants registered at general practices in Wessex, West of England, East Midland, Thames Valley and South Midlands. Practices will be recruited through the local Clinical Research Networks in England. We aim to recruit practices that are broadly representative of UK primary care in terms of practice size and socio-demographics.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

Participants will be eligible for inclusion in trial-YP if:

- They are aged 13-25 years with eczema
- They were identified from GP records as having eczema and have obtained a prescription for eczema treatment in the past 12 months
- They have a POEM score greater than 5 to include mild to severe eczema, but exclude those with very mild or inactive eczema to avoid floor effects
- They have internet access

Participants will be eligible for inclusion in trial-PC if:

- They are a parent / carer of a child aged 0-12 years with eczema

- Their child was identified from GP records as having eczema and has obtained a relevant prescription in the past 12 months
- Their child has a POEM score greater than 5 to include mild to severe eczema, but exclude those with very mild or inactive eczema
- They have internet access

Only 1 person per household will be able to take part in one of the trials. If a parent/carer in trial-PC has more than one child who meets the inclusion criteria they will be asked to specify one child to participate.

2.4.2. Exclusion criteria

Potential participants will be excluded from trial-YP and trial-PC if:

- They are unable to give informed consent
- They are unable to read and write English as the intervention content and outcome measures are in English
- They have taken part in another eczema study in the past 3 months
- They took part in think aloud interviews as part of ECO intervention development. Qualitative interviewees who did not view intervention materials will not be excluded.

2.5. Description of interventions

Usual care group

Participants randomised to usual care will continue to receive their usual medical advice and prescriptions. They will not be prevented from seeking additional online support but will not be supported in doing so by the study team and will not have access to the trial online interventions during the trial. Participants allocated to the usual care group will receive access to either intervention-YP or intervention-PC (depending on which trial they are in) after 52-week follow-up.

Intervention-YP and intervention-PC groups

Participants randomised to the intervention group will receive access to an online behavioural intervention to support eczema self-care in addition to usual eczema care, as above. The online interventions target core behaviours linked to eczema treatment use (regular use of emollients and appropriate use of topical corticosteroids), eczema irritants and triggers, scratching, and emotional management. The interventions use behavioural techniques to support eczema self-care by building on aspects like knowledge, skills, self-efficacy, social support, and addressing environmental factors such as social and physical opportunity.

Intervention-YP has been developed for people aged 13 to 25 years with eczema. The intervention covers a wide range of topics that are important to people with eczema, as well as additional sections that are important particularly to this age group, such as information about finances, school / university /work, and cosmetics.

Intervention-PC has been developed for parents of children aged 0 to 12 years with eczema. This intervention covers the same wide range of topics relevant to eczema, as well as sections that are specifically relevant to parents and co-management of eczema, such as transitioning to co-management, dealing with child resistance, and managing your child's eczema at nursery and school.

2.6. Randomisation procedures

Eligible participants will be randomised online to either 1) usual eczema care or 2) online intervention plus usual care through LifeGuide software. Randomisation will be carried out in blocks and stratified by age (13-17; 18-25 (trial-YP), and 0-5; 6-12 (trial-PC), baseline eczema severity (POEM scores 6-7; 8-16; 17-28) and recruitment site as these may influence how participants engage with the interventions.

2.7. Sample size and justification

The sample sizes for trial-YP and trial-PC are based on 4-weekly POEM scores using repeated measures over the first 24 weeks of the trial, seeking to detect a minimum clinically important difference (MCID) of 2.5 points between groups (s.d. 6.5). Assuming a correlation between repeated measures of 0.70 (not including baseline correlation and assuming no treatment*time interaction), with 90% power and 5% significance, this requires a total sample size of 121 per group in each of the two trials. Allowing for 20% loss to follow up gives a total sample size of 303 in each of the two trials.

2.8. Blinding

Participants will not be blind to their allocation group, but the trial statistician and TMG will remain blinded and prior belief in the likely benefit of the interventions will be assessed at baseline.

2.9. Outcome measures

All participant reported outcome measures and intervention usage data will be collected online, via LifeGuide software. Outcome measures are very similar across trial-YP and trial-PC, where there are any differences these are highlighted. Harmonising Outcome Measures for Eczema (HOME) core measures were assessed, except EASI due to no face-to-face assessment. See Table 1 for schedule of observations. Missing questionnaires (at 4, 8, 12, 24 and 52 weeks) will be followed up by phone, text or email.

2.9.1. Primary outcome

The primary outcome for both trials is the difference in eczema severity between the intervention and usual care group as measured by POEM (Patient-Oriented Eczema Measure) every 4 weeks over 24 weeks [1,2]. The estimand is therefore the main treatment effect from a linear mixed model. 24 weeks has been shown in previous NIHR-funded eczema trials to be a sufficient duration to capture the chronic-relapsing nature of eczema. Loss to follow-up is likely to be greater at 52 weeks – this is particularly important for a trial in which consent and follow-up assessments are all conducted online.
POEM includes 7 questions about the frequency of eczema symptoms over the previous week that are summed to give a score from 0 (no eczema) to 28 (worst possible eczema). POEM is a patient reported outcome that measures symptoms that are important to the patient and takes around 1 minute to complete. POEM can be completed by young people and children or by proxy (carer report), demonstrates good validity, repeatability and responsiveness to change [3]. POEM has been recommended as a core outcome measure for symptoms by the international Harmonising Outcome Measures for Eczema group [4].

2.9.2. Secondary outcomes

Secondary outcomes include

- Difference in POEM scores captured 4-weekly over 52 weeks.
- Quality of Life will be measured at baseline, 24 and 52 weeks in both trials. In trial-YP, Quality of Life will be measured using the EQ-5D-5L self-completed by the young person. In trial-PC, Quality of Life will be measured by proxy using the Child Health Utility - Nine Dimensions (CHU-9D) for those children aged 2 to 12 years.
- Eczema control will be measured by RECAP (Recap for atopic eczema patients) measured at baseline, 24 and 52 weeks [5]. RECAP is scored in the same way as the POEM.
- Itch intensity measure (worst itch in last 24 hours) at baseline, 24 and 52 weeks [6] using a numeric rating scale, is validated in adults only and will therefore be collected in trial-YP only.

Other baseline variables:

- Prior belief about the effectiveness of the intervention.
- Use of other websites for eczema.

2.9.3 Process measures

Process measures include:

- Self-reported frequency of use of emollients ((ii) how many days used in past week and (ii) how many times per day) and topical corticosteroids or topical calcineurin inhibitors (how many days used in past week) at baseline, 24 and 52 weeks.
- Enablement, the self-perceived ability to understand and cope with health issues, will be measured using the Patient Enablement Instrument (PEI) at baseline, 24 and 52 weeks [7]. This is a 6-item scale where "much better/more" scores 2 points, "better/more" scores 1 point and "same or less" or "not applicable" scores 0 points. This leads to total sum ranging from 0 to 12, with higher scores indicating higher levels of enablement.
- Self-reported barriers to adherence will be measured using the Problematic Experiences of Therapy Scale (PETS) [8]
- Intervention usage data for each participant will be automatically recorded by LifeGuide Software for the duration of the 52-week trial period.
- Health service use and medication use will be measured by medical notes review for the 3-month period prior to baseline and the whole 52-week trial period.

2.10. Internal pilots

The first 3-months of participant recruitment were an internal pilot phase to test trial procedures, which mirrored the main trial protocol exactly. We assessed study uptake, recruitment and follow-up procedures, randomisation, and participant engagement in accessing the intervention. Success criteria for the pilot phase are listed in the full protocol.

2.11. Interim analysis

No interim analysis is planned.

3. General Analysis Considerations

3.1. Analysis samples

The main approach for the analysis of both trials will be on an intention to treat basis defined as analysing participants as randomised, regardless of the adherence with their allocated group. For this population, missing baseline data will be imputed as set out in section 3.2 below but there will be no imputation of missing data for any primary or secondary outcomes.

Sensitivity analyses will explore the effect of missing data (using multiple imputation), prior belief in the effectiveness of the intervention and adherence with the allocated group based on reported use of other relevant websites. See section 6.2 for further details.

3.2. Procedures for missing data

Missing items in questionnaires

For missing items on the POEM questionnaire, the total score will be calculated according to guidance on the Centre for Evidence Based Dermatology website:

- If one question is left unanswered this is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored.

See http://www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx.

Missing baseline data

POEM is a compulsory measure at baseline so no scores should be missing

Missing outcome data

Mixed models (for repeated measures) will be used as the primary approach to analyse 4-weekly POEM, allowing participants to contribute data for all the time points for which they have completed a 4-weekly questionnaire.

The structure and pattern of missing data will be examined, if appropriate, and a sensitivity analysis based on data imputed using a multiple imputation model presented. Data will be imputed using a chained equations approach with a model including all outcome variables, baseline POEM scores, randomisation group, and covariates included in the primary analysis model (see below).

There will be no imputation for any of the secondary outcomes.

4. Description of participant characteristics

4.1. Disposition

For each trial, the flow of patients will be summarised in a CONSORT diagram that will include the numbers assessed for eligibility, reasons for exclusion, numbers randomised to the two treatment groups, numbers receiving the allocated intervention, losses to follow up and the numbers analysed. These diagrams are set out in the Appendix

4.2. Baseline characteristics

For each trial, the baseline characteristics of the two groups with respect to sociodemographic characteristics, prior belief in the intervention and online resource use (websites or apps) for eczema, prior use of treatments, eczema severity (POEM) and quality of life (EQ5D, CHU-9D) will be summarised.

Continuous data will be summarised in terms of the mean, standard deviation, and number of observations or, where skewed, median and lower & upper quartiles. Binary/categorical data will be summarised in terms of frequency counts and percentages.

5. Assessment of Study Quality

5.1. Data management and validation

Data checks will be carried out by the statistician when preparing the data for analysis in Stata. These checks will include missing values, out of range values, illogical values and invalid response.

No methods will be used to handle outliers in the data, except in the regression models. If outliers (more than 1.5*interquartile range (IQR) above upper quartile or less than 1.5*IQR below lower quartile) are found, then firstly the source data will be checked. If the source data is correct, then a sensitivity analysis will be performed excluding them from the analysis.

5.2. Protocol deviations

A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of a study inconsistent with the protocol, consent documents or other study procedures. Of particular importance are major deviations (violations) which may expose participants to increased risk; compromise the integrity of the entire study or affect participant eligibility. Protocol deviations, as reported on the eCRF page, will be listed with information on treatment group and the type of deviation. Full details of the protocol deviations will also be listed. Failure to engage with the randomised intervention will not be taken as a protocol deviation and neither will use of other websites by participants in the control group.

6. Analysis of Effectiveness

The analysis approach is the same for both trials.

Analyses will be performed using Stata version 13 or above. All tests will be two-tailed with point estimates, 95% confidence intervals and exact p-values.

Analyses using regression models will adjust for the stratification factors used in the randomisation. No formal adjustment for multiple significance testing will be applied. The primary approach for analysis will be as randomised without imputation of missing data.

6.1. Primary analysis

In both trials, the primary analysis for the total POEM score will be performed using a generalized linear mixed model (GLMM) framework with observations at weeks 1 through to 24 (level 1) nested within participants (level 2). Unadjusted results will be reported as well as results adjusting for baseline POEM, recruitment region and the following covariates which have been pre-specified as possible confounders: age, gender, ethnicity, prior belief in the intervention, education (or carer education for children) and prior use of a website or app for information or advice about the child/young person's eczema.

The linear mixed model will use all the observed data, and implicitly assumes that missing POEM scores are missing at random given the observed data.

As there may not be a constant treatment effect over time, a treatment/time interaction will be modelled and included if significant, with time treated as a random effect. The model will include a random effect for centre (random intercept) and patient (random intercept and slope on time) to allow for between patient and centre differences at baseline and between patient differences in the rate of change over time (if significant), and fixed effects for baseline covariates. An unstructured covariance matrix will be used.

The assumptions of the normality of the residuals from the fixed part of the model and the normality of the random effects at the cluster level will be checked. Appropriate transformations will be considered if there is some suggestion that the assumptions for the linear mixed model may not be met.

6.2. Sensitivity analyses for the primary outcome

6.2.1 Sensitivity analysis for missing data

Sensitivity analyses for missing data to explore departures from the missing at random assumption used in the primary analysis will be performed. If appropriate, multiple imputation will be used to impute missing 4-weekly POEM values under a missing at random assumption with an imputation model including baseline values and questionnaire information. The analysis specified above will repeated to explore if the findings from this sensitivity analysis are similar to the main analysis.

6.2.2 Sensitivity analysis for adherence with allocation

To explore the effect of adherence to randomisation, we will perform a CACE analysis (using randomisation as the instrument) to obtain the intervention effect by engagement with core information in intervention. This will give an estimate of the effect for participants who use the intervention(s) and will be compared to the estimate of the effect from the as randomised analysis which is more useful for estimating the effect of prescribing the online intervention.

6.3. Analysis of secondary outcomes

For the analysis of secondary outcomes, repeated measures analysis in line with that used for the primary outcome will be used for the 4-weekly POEM measure up to 52 weeks. For other secondary outcomes, linear regression will be used for continuous outcomes if the assumptions are met. Otherwise non-parametric analyses will be used. Logistic regression will be used for dichotomous outcomes and a suitable count model, as determined by goodness of fit measures, for count data. All analyses will control for stratification variables, baseline scores and potential confounders.

6.4 Analysis of process outcomes

For analysis of process outcomes, linear regression will be used for continuous outcomes, controlling for stratification, baseline scores and potential confounders. An analysis plan for the process evaluation will be developed separately.

7. Analysis of Safety

7.1 Adverse events

Any adverse events will be tabulated by allocated group.

8. Exploratory analysis

Although we are not powered to look at subgroups, we will explore the impact of key subgroups that could plausibly modify intervention effectiveness:

- Mode of follow up (online/telephone)
- Age of person with eczema – 0-4 years vs 5-12 years in PC trial; 13-17 years vs 18-25 years in YP trial
- baseline severity score – POEM score at baseline of: 5–7 (clear/mild), 8–16 (moderate); 17–28 (severe/very severe)
- baseline use of leave on emollient - 0-4 days per week versus 5-7 days per week
- baseline use of TCS– none/mild TCS vs moderate or stronger
- Pre- vs during Covid-19 pandemic – before vs after 11 March 2019
- prior belief in the effectiveness of the intervention (1-3=low belief in effectiveness, 4-6 = moderate belief in effectiveness and 7-9=high belief in effectiveness)
- Prior use of other relevant apps/websites

For this exploratory analysis, estimates of the interaction between subgroup and intervention will be provided with 95% confidence intervals and the estimates of the intervention effect when the subgroup is selected. Clear evidence of benefit in a subgroup will require the interaction term for that subgroup to be significant at the 5% level. Although a formal adjustment for multiplicity will not be carried out, the results will be interpreted cautiously, as at least 1 significant result might be expected by chance [10].

9. Other analysis

The cost-effectiveness evaluation of the intervention as specified in the protocol will be conducted by Professor Tracey Sach, and will be specified in a separate Health Economics analysis plan. The team will also develop a separate analysis plan for the process evaluation.

References

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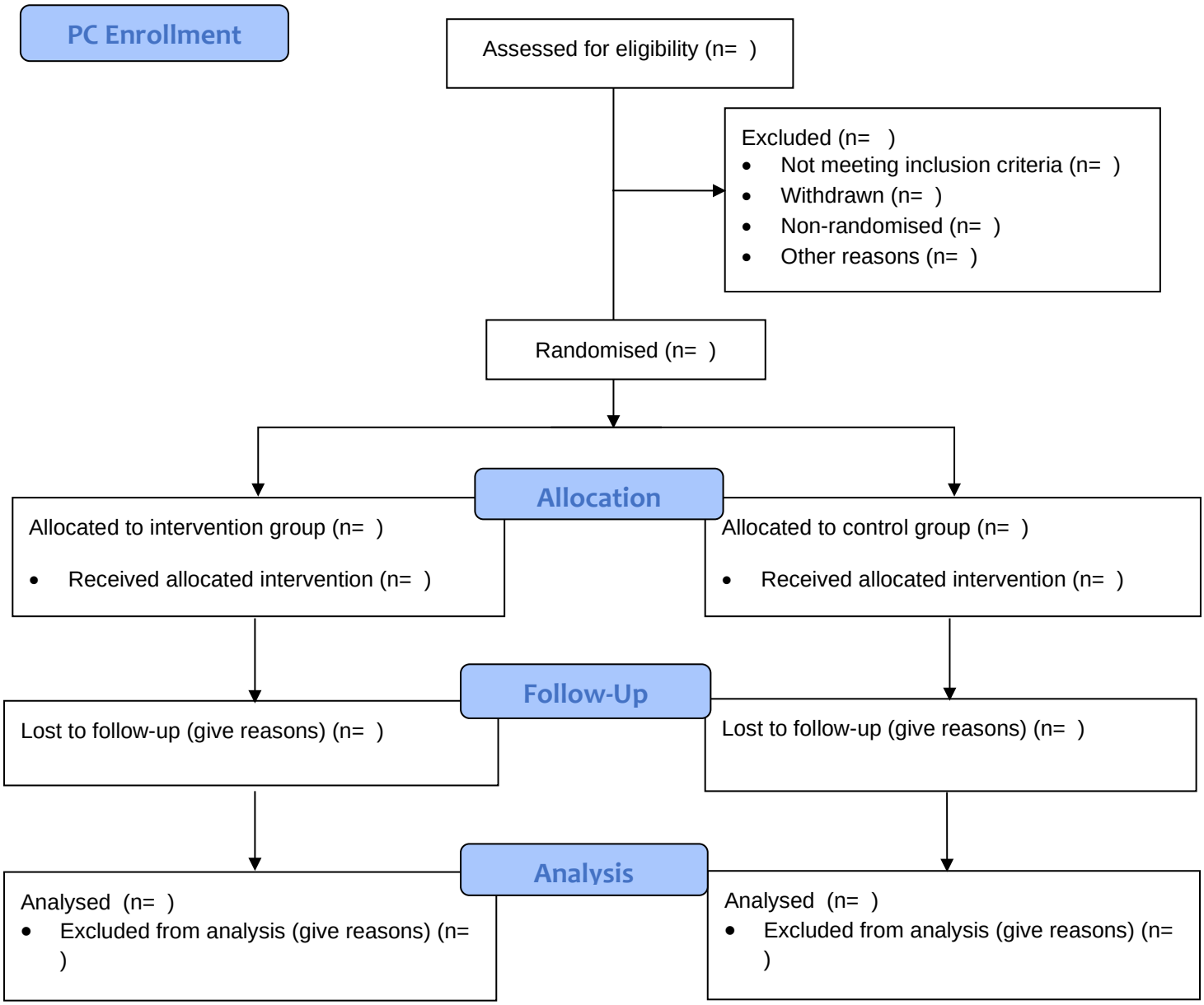
Outcomes collected	Baseline	4-Weekly for 52 weeks	24 weeks	52 Weeks (end of study)
Participant completed				
POEM	✓	✓		
Demographics	✓			
CHU-9D (Trial-PC for parents / carers of children aged 2-12 only)	✓		✓	✓
EQ-5D-5L (Trial-YP only)	✓		✓	✓
Patient enablement Instrument (PEI)	✓		✓	✓
Problematic Experiences of Therapy Scale (PETS)	✓		✓	✓
Treatment use self-report	✓		✓	✓
Prior belief about effectiveness	✓			
Online resource use	✓			
Long-term control (Recap for atopic eczema patients	✓		✓	✓
Itch intensity measure (trial-YP only)	✓		✓	✓
Research team completed				
Medical notes review for medication use, service use, and referrals				✓ (including 3 months pre-baseline period)

Table 1. Schedule of observations.

Appendix 1

ECO Consort diagram – Parents and Carers (PC)



ECO Consort diagram – Young People (YP)