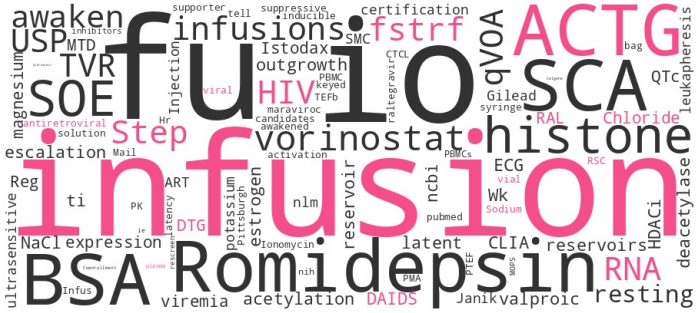
Analysis of 94_NCT01933594_Prot_001.pdf

This is a LOW-risk HIV trial

The risk level is derived from a total score of **58** on a 100-point scale.
Word cloud of informative terms from the document:



Key information about this protocol

Parameter	Value (approved by user if applicable)	Value found by AI	Confidence
Page count	140 pages		
Word count	49737 words		
Average words per page	355.3 words		
Condition	HIV	HIV	79.6%
Phase	1.5	1.5	
Has the Statistical Analysis Plan been completed?	yes	yes	59.0%
Has the Effect Estimate been disclosed?	yes	yes	48.8%
Number of subjects	12	12	
Countries of investigation	United States, one or more unspecified countries	United States, one or more unspecified countries	
Trial uses simulation for sample size?	no	no	0.0%

Risk calculation spreadsheet

The table below shows how the risk of this protocol was calculated. Protocols are scored according to a simple linear formula between 0 and 100, where 100 would be a perfect low-risk protocol and 0 would be a high-risk protocol. Each parameter extracted in the table on the left is entered into a spreadsheet and contributes to the scoring with an associated weight. For example, by far the strongest indicator that a protocol is low-risk is the presence of a statistical analysis plan.

Parameter	Value	Weight	Score	Excel Formula
94_NCT01933594_Prot_001.pdf				
Trial is for condition	HIV			
Number of subjects	12			
Lower tertile number of subjects for phase and pathology	80			
Upper tertile number of subjects for phase and pathology	280			
Number of arms	3	2.0	6	=B7*C7
Trial phase	1.5	5.0	7.5	=B8*C8
SAP completed?	1	26.0	26	=B9*C9
Effect Estimate disclosed?	1	16.0	16	=B10*C10
Number of subjects low/medium/high	0	10.0	0	=B11*C11
International?	1	10.0	10	=B12*C12
Simulation?	0	10.0	0	=B13*C13
Constant	1	-7.0	-7	=B14*C14
Total score (50-100=low risk, 0-40=high risk)			58	=MIN(100,SUM(D7:D14))

Risk level			LOW	=IF(D15<40,"HIGH",IF(D15<50,"MEDIUM","LOW"))

Sample size tertiles

The model characterises trials as small, medium and large according to the number of participants. Since early phase trials are smaller than later trials, tertiles are used to define what counts as e.g. a small HIV Phase I trial. The table of tertiles is given below.

Phase	HIV lower tertile	HIV upper tertile	TB lower tertile	TB upper tertile
0.0	10	15	10	15
0.5	40	130	30	60
1.0	40	130	30	60
1.5	80	280	40	80
2.0	100	300	50	100
2.5	1000	2000	500	1500
3.0	1000	2000	500	1500
4.0	3000	4000	3000	4000

How the protocol was analysed

This is a log of the analysis of the text which was carried out by the protocol analysis tool, with an explanation of the scoring. Converting PDF to text...

Taking file from dropdown 94_NCT01933594_Prot_001.pdf.

The PDF document was converted to text in 0.01 seconds and contained 140 pages.
Splitting the document into words (tokens)...

There were 49737 words in the document.
Searching for a likely pathology...

This looks like an HIV trial.
Searching for a phase...

This looks like a Phase 1.5 trial.
Neural network thought it was a Phase 1.5 trial.
Searching for a statistical analysis plan...

It does not look like the protocol contains a statistical analysis plan.
Testing top pages for SAP with document level SAP Naive Bayes model to refine SAP prediction.
Document level Naive Bayes model found SAP score 1 with score 0.5896859191453976.
Searching for an effect estimate...

Identified probable effect estimate.
Naive Bayes arms prediction probabilities: {'1': 0.15118132734068362, '2': 0.42239348119637854, '3+': 0.42642519146293606}.
Spacy arms prediction probabilities: {'1': 8.177267890596696e-12, '2': 1.6423006617832803e-14, '3+': 1.0}.
Searching for a number of arms...

No explicit mention of arms found.
Running Random Forest classifier for number of subjects...

Searching for a number of subjects...

It looks like the trial has 12 participants.
Searching for the countries of investigation...

It looks like the trial takes place in 1 country: US
Neural network found that trial country is likely to be USCA.
Neural network for is trial international? output: 1.
Naive Bayes model for is trial international? output: 0.
Ensemble model output: {"prediction": ["US", "XX"], "score": {"US": 0.86, "XX": 0.51, "PR": 0.2525, "AU": 0.1}}
Searching for any mentions of simulation...

It does not look like the authors used simulation for sample size.
The NLP analysis ran in 5.36 seconds.
Calculating the score:
Start at -7.0 points.
Add 6.0 points because the trial has 3 arms.
Add 7.5 points because the trial is Phase 1.5.
Add 26.0 points because the trial included a Statistical Analysis Plan (SAP).
Add 16.0 points because the authors disclosed an effect estimate.

Add 10.0 points because the trial takes place in multiple countries.
Total score is 58.
Scores between 50 and 100 are low risk, scores between 40 and 50 are medium risk, and scores between 0 and 40 are high risk.
Risk is therefore LOW
Score calculated in 0.02 seconds.

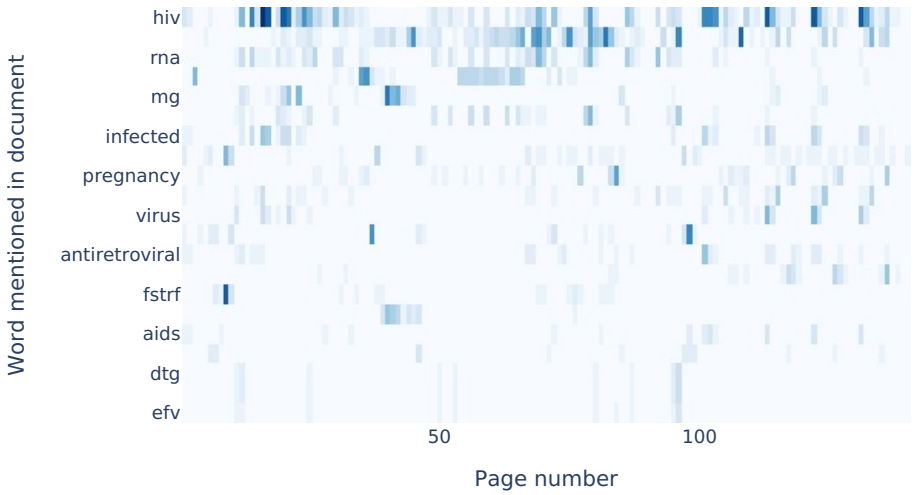
Explanation: Overview Of Word Counts By Page

Word counts of each page. Page count: 140, word count: 49737

Explanation: Condition

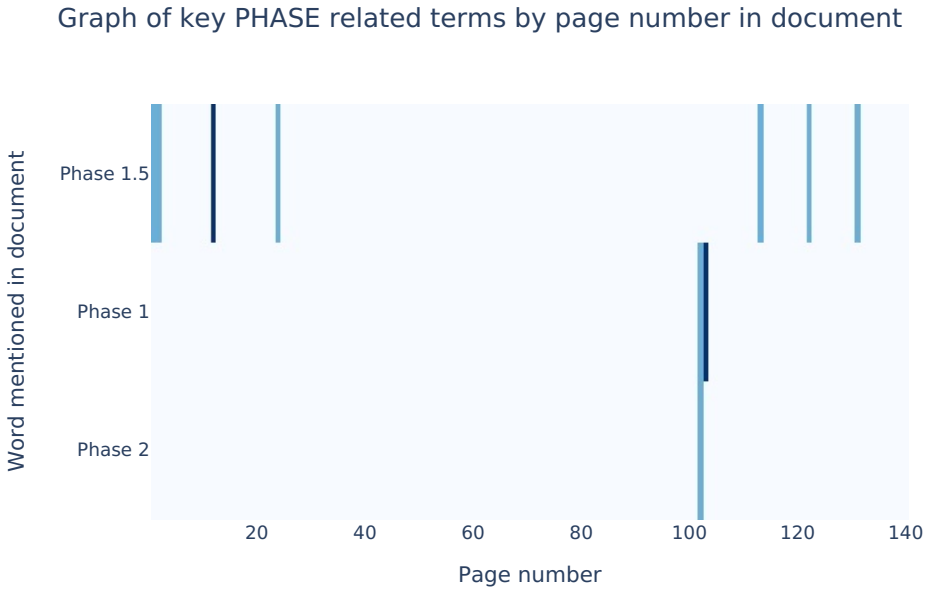
Condition identified: **HIV** . Confidence: 79.6%. The heat map below shows you key terms related to the condition and which pages they occurred on throughout the document.

Graph of key HIV related terms by page number in document



Explanation: Phase

Where was the phase mentioned in the document? The graph below shows possible phases and which pages they were mentioned on. The document is most likely to be **Phase 1.5** .



Possible mentions of PHASE in the document

Phase 1.5

[Li('Page 1: a5315 a phase i ii study of romidepsin in hiv infected adults with suppressed viremia on antiretroviral therapy to assess '), Li('Page 2: a5315 final version 4.0 06 07 18 a phase i ii study of romidepsin in hiv infected adults with suppressed viremia on antiretroviral therapy to assess '), Li('Page 12: 12 a5315 final version 4.0 06 07 18 schema a5315 a phase i ii study of romidepsin in hiv infected adults with suppressed viremia on antiretroviral therapy to assess '), Li('Page 12: therapy to assess safety tolerability and activation of hiv 1 expression design a5315 is a phase i ii double blinded randomized placebo controlled dose escalation study to evaluate the safety and efficacy of '), Li('Page 24: leukapheresis has been replaced with a blood collection 3.0 study design this is a multicenter phase i ii safety dose escalation and preliminary efficacy study the study will be conducted in two stages '), Li('Page 113: cohorts 1 and 2 in protocol a5315 final version 4.0 dated 06 07 18 a phase i ii study of romidepsin in hiv infected adults with suppressed viremia on antiretroviral therapy to assess '), Li('Page 122: consent for cohort 3 in protocol a5315 final version 4.0 dated 06 07 18 a phase i ii study of romidepsin in hiv infected adults with suppressed viremia on antiretroviral therapy to assess '), Li('Page 131: consent for cohort 4 of protocol a5315 final version 4.0 dated 06 07 18 a phase i ii study of romidepsin in hiv infected adults with suppressed viremia on antiretroviral therapy to assess')]

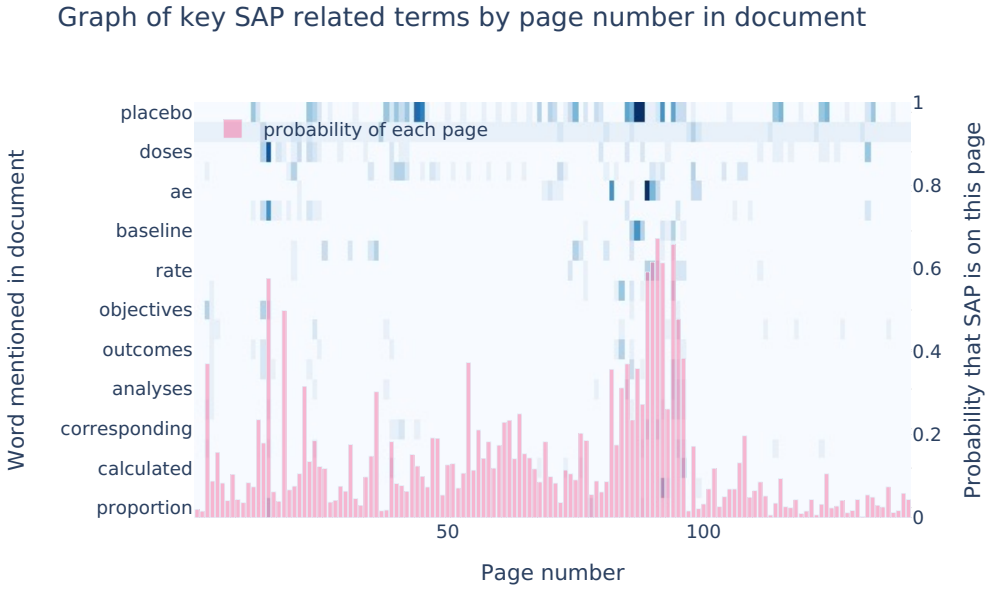
Phase 2 Page 102: nature 2012 487 7408 482 5 24 piekarz rl frye r prince hm et al phase 2 trial of romidepsin in patients with peripheral t cell lymphoma blood 2011 117 5827 34

Phase 1

[Li('Page 102: 33 5 777 90 29 children s oncology group fouladi m furman wl et al phase i study of depsipeptide in pediatric patients with refractory solid tumors a children s oncology group '), Li('Page 103: 1 14 3 826 32 31 marshall jl rizvi n kauh j et al a phase i trial of depsipeptide fr901228 in patients with advanced cancer j exp ther oncol 2002 nov '), Li('Page 103: nov dec 2 6 325 32 32 sandor v bakke s robey rw et al phase i trial of the histone deacetylase inhibitor depsipeptide fr901228 nsc 630176 in patients with refractory neoplasms')]

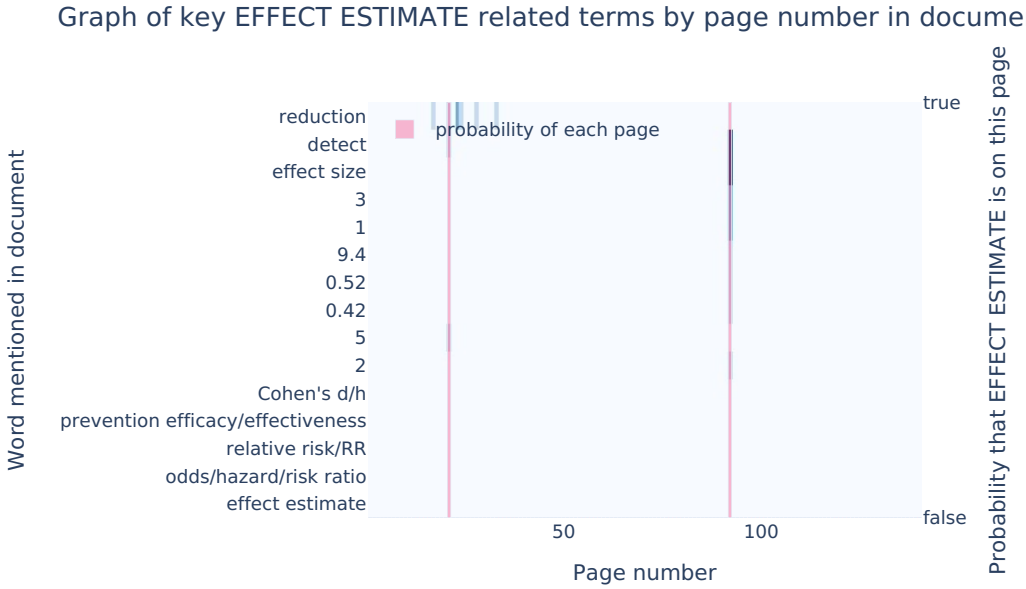
Explanation: SAP

Which pages contained highly statistical content and were likely to be part of the SAP? Graph of a selection of key statistical terms by page number, overlaid with page-level probabilities (in pink).



Explanation: Effect Estimate

Where was an effect estimate found in the document? The graph below shows some candidate effect estimates and a selection of key terms by page number, overlaid with page-level probabilities (in pink). The protocol is 48.8% likely to contain an effect estimate.



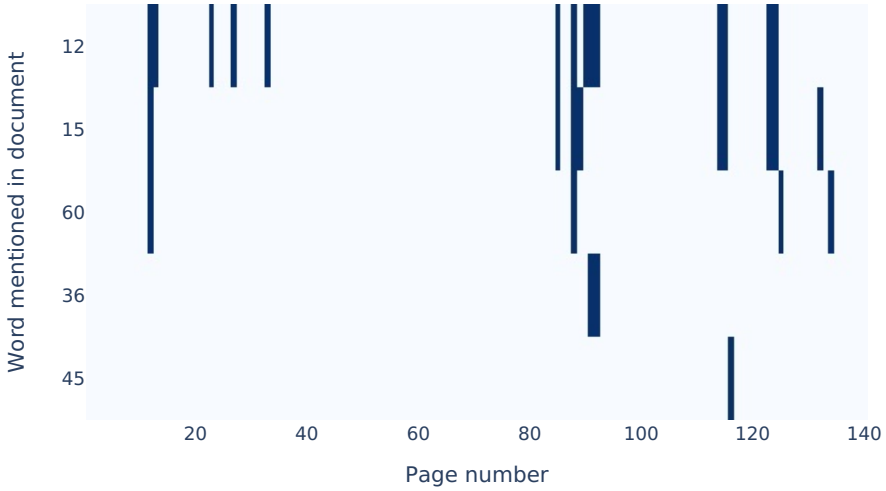
Possible mentions of EFFECT ESTIMATE in the document

1 Page 92: be no change in HIV 1 RNA in the placebo group with 36 active and 9 placebos combined in Cohorts 1 3 the study will have 80% power to detect a difference of 0.38 log10 copies million CD4 cells in
2 Page 92: assay limit The following table presents the detectable effect size based on various sample sizes and standard deviations Table 9.4 2 1 Detectable effect sizes based on various sample sizes and assumed standard deviations Estimated standard deviation of log10 change
3 Page 92: no change in HIV 1 RNA in the placebo group with 36 active and 9 placebos combined in Cohorts 1 3 the study will have 80% power to detect a difference of 0.38 log10 copies million CD4 cells in the
5 Page 92: TVR compared to 6 fold with qVOA 38 The TVR assay is also more efficient more sensitive rare censoring and 5 fold less costly than qVOA The goal of A5315 is to detect any effect of RMD on the total
0.52 Page 92: n = 12 with the combined placebo group n = 9 the study will have 80% power to detect a 0.52 log10 increase in RNA by SCA The sample size estimation includes an adjustment of 15% for the potential loss
0.42 Page 92: RMD group and n = 9 in the combined placebo group the study will have 80% power to detect a 0.42 log10 increase in HIV 1 RNA by SCA using a two sided Wilcoxon rank sum test at 5% level
9.4 Page 92: below assay limit The following table presents the detectable effect size based on various sample sizes and standard deviations Table 9.4 2 1 Detectable effect sizes based on various sample sizes and assumed standard deviations Estimated standard deviation of log10

Explanation: Number Of Subjects

Which pages contained terms relating to the number of subjects? The sample size appears to be 12 with confidence 47.0%.

Graph of key NUMBER OF SUBJECTS related terms by page number in docume



Possible mentions of NUMBER OF SUBJECTS in the document

12

[Li('Page 12: cohorts and randomized 4 1 to receive RMD or placebo as shown below Cohort 1 12 participants will receive 0.5 mg m2 RMD in 0.9% saline 3 participants will receive placebo in '), Li('Page 12: m2 RMD in 0.9% saline 3 participants will receive placebo in 0.9% saline Cohort 2 12 participants will receive 2 mg m2 RMD in 0.9% saline 3 participants will receive placebo in '), Li('Page 12: m2 RMD in 0.9% saline 3 participants will receive placebo in 0.9% saline Cohort 3 12 participants will receive 5 mg m2 RMD in 0.9% saline 3 participants will receive placebo in '), Li('Page 13: 0.9% saline 13 A5315 FINAL Version 4.0 SCHEMA Cont d 06 07 18 Cohort 4 12 participants will receive a total of 20 mg m2 RMD in 0.9% saline 5 mg m2 '), Li('Page 23: by the SMC before enrollment to Cohort 4 is permitted Safety data from at least 12 evaluable Cohort 3 participants should be sufficient to determine if it is safe to proceed with '), Li('Page 23: 6 week period As in the three earlier cohorts the randomization will be 4 1 12 participants randomized to receive RMD and 3 to receive placebo infusions Three RMD infusions of 5 '), Li('Page 27: oral report of her partner s status should be written into the source documents 4.1 12 Female candidates of reproductive potential must refrain from participating in active attempts to become pregnant and '), Li('Page 33: score 80 at pre entry between 3 and 14 days prior to study entry 4.3 12 Men and women age 18 years 4.3 13 Ability and willingness to provide written informed consent '), Li('Page 85: 3 ie if dose escalation criteria are met Each cohort of 15 participants consists of 12 evaluable participants receiving RMD and 3 receiving placebo single dose in Cohorts 1 3 and multiple '), Li('Page 88: cohort will open sequentially Within each cohort 15 participants will be randomized to receive RMD 12 participants or placebo 3 participants Randomization will use a permuted block method without institutional balancing or '), Li('Page 88: Size and Accrual The total sample size of this study will be 60 evaluable participants 12 evaluable active plus 3 evaluable placebo controls per dosing cohort if all four cohorts are enrolled '), Li('Page 90: 07 18 Table 9.4 1 1 Probabilities of dose escalation under various assumed true rates n = 12 on RMD True rate of Grade 3 AE probably or possibly related to study Rx '), Li('Page 90: 1 a block size of 5 has been used Based on this method with a total of 12 participants enrolled in Cohort 3 there will be 9 or 10 participants randomized to receive '), Li('Page 90: block size of 5 has been used Based on this method with a total of 12 participants enrolled in Cohort 3 there will be 9 or 10 participants randomized to receive RMD '), Li('Page 91: With N = 10 the study still provides a low probability although higher than with N = 12 of dose escalation when the true event rates are unacceptable For example for the same '), Li('Page 91: rates as above the probability of dose escalation is 0.18 ie 18% vs 0.12 with N = 12 and the corresponding probability of not dose escalating and correctly concluding the dose unsafe is '), Li('Page 91: N = 9 the probabilities of dose escalation are larger than in the setting with N = 12 as expected For example for the same assumed rates as above the probability of dose '), Li('Page 91: rates as above the probability of dose escalation is 0.22 ie 22% vs 0.12 with N = 12 and the corresponding probability of not dose escalating and correctly concluding the dose unsafe is '), Li('Page 92: sum test at 5% level For the secondary comparison of a given RMD dose group n = 12 with the combined placebo group n = 9 the study will have 80% power to '), Li('Page 114: in Group 1 They will receive 0.5 mg m2 of RMD or placebo By chance 12 participants will receive RMD and 3 will receive placebo If this amount of RMD solution is '), Li('Page 115: participants in Group 2 will receive 2 mg m2 of RMD or placebo By chance 12 participants will receive RMD and 3 will receive placebo If this amount of RMD solution is '), Li('Page 115: participants in Group 3 will receive 5 mg m2 of RMD or placebo By chance 12 participants will receive RMD and 3 will receive placebo Neither you nor the study staff will '), Li('Page 123: in Group 1 They will receive 0.5 mg m2 of RMD or placebo By chance 12 participants will receive RMD and 3 will receive placebo If this 124 A5315 FINAL Version 4.0 '), Li('Page 124: participants in Group 2 will receive 2 mg m2 of RMD or placebo By chance 12 participants will receive RMD and 3 will receive placebo If this amount of RMD solution is '), Li('Page 124: participants in Group 3 will receive 5 mg m2 of RMD or placebo By chance 12 participants will

receive RMD and 3 will receive placebo Neither you nor the study staff will')]

15

[Li('Page 12: of single dose and multiple dose administration of romidepsin RMD Four cohorts 1 4 of 15 participants each will be sequentially enrolled into the study depending on safety outcomes which will determine '), Li('Page 12: study duration for Cohort 4 participants will be 48 weeks SAMPLE SIZE 60 evaluable participants approximately 15 evaluable participants in each cohort POPULATION HIV infected adults at least 18 years of age '), Li('Page 12: study duration for Cohort 4 participants will be 48 weeks SAMPLE SIZE 60 evaluable participants approximately 15 evaluable participants in each cohort POPULATION HIV infected adults at least 18 years of age with '), Li('Page 12: duration for Cohort 4 participants will be 48 weeks SAMPLE SIZE 60 evaluable participants approximately 15 evaluable participants in each cohort POPULATION HIV infected adults at least 18 years of age with '), Li('Page 85: is established in Cohort 3 ie if dose escalation criteria are met Each cohort of 15 participants consists of 12 evaluable participants receiving RMD and 3 receiving placebo single dose in Cohorts '), Li('Page 88: in Cohort 4 9.3 Randomization and Stratification Each cohort will open sequentially Within each cohort 15 participants will be randomized to receive RMD 12 participants or placebo 3 participants Randomization will use '), Li('Page 89: above and under various enrollment projections i e if at least 12 but fewer than 15 participants are enrolled into a cohort In the tables the column True rate of Grade 3 '), Li('Page 114: study you will be placed in one of three groups Each group will have a total of 15 participants 12 will receive RMD and 3 will receive the placebo salt solution that does '), Li('Page 114: will be placed in one of three groups Each group will have a total of 15 participants 12 will receive RMD and 3 will receive the placebo salt solution that does not '), Li('Page 114: placebo If this amount of RMD solution is found to be safe then the next 15 participants will enter into Group 2 115 A5315 FINAL Version 4.0 06 07 18 The 15 '), Li('Page 115: participants will enter into Group 2 115 A5315 FINAL Version 4.0 06 07 18 The 15 participants in Group 2 will receive 2 mg m2 of RMD or placebo By chance 12 '), Li('Page 115: placebo If this amount of RMD solution is found to be safe then the next 15 participants will enter into Group 3 The 15 participants in Group 3 will receive 5 mg '), Li('Page 115: found to be safe then the next 15 participants will enter into Group 3 The 15 participants in Group 3 will receive 5 mg m2 of RMD or placebo By chance 12 '), Li('Page 123: study you will be placed in one of three groups Each group will have a total of 15 participants 12 will receive RMD and 3 will receive the placebo salt solution that does '), Li('Page 123: will be placed in one of three groups Each group will have a total of 15 participants 12 will receive RMD and 3 will receive the placebo salt solution that does not '), Li('Page 124: 06 07 18 amount of RMD solution is found to be safe then the next 15 participants will enter into Group 2 The 15 participants in Group 2 will receive 2 mg '), Li('Page 124: found to be safe then the next 15 participants will enter into Group 2 The 15 participants in Group 2 will receive 2 mg m2 of RMD or placebo By chance 12 '), Li('Page 124: placebo If this amount of RMD solution is found to be safe then the next 15 participants will enter into Group 3 The 15 participants in Group 3 will receive 5 mg '), Li('Page 124: found to be safe then the next 15 participants will enter into Group 3 The 15 participants in Group 3 will receive 5 mg m2 of RMD or placebo By chance 12 '), Li('Page 132: this study we tested three doses of RMD in each of three groups of 12 15 people These people received a one time infusion of one of three doses of RMD or')]

36

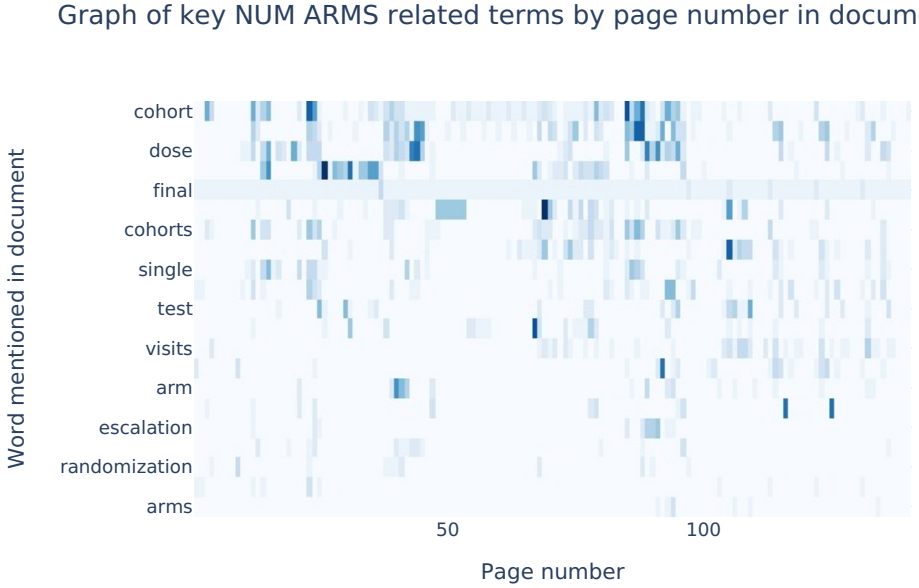
[Li('Page 91: protocol there will be n = 9 participants in the combined placebo control group and n = 36 participants in the combined RMD group 92 A5315 FINAL Version 4.0 06 07 18 The '), Li('Page 91: there will be n = 9 participants in the combined placebo control group and n = 36 participants in the combined RMD group 92 A5315 FINAL Version 4.0 06 07 18 The study '), Li('Page 91: will be n = 9 participants in the combined placebo control group and n = 36 participants in the combined RMD group 92 A5315 FINAL Version 4.0 06 07 18 The study '), Li('Page 92: no change in HIV 1 RNA in the placebo group with a sample size of n = 36 in the combined RMD group and n = 9 in the combined placebo group the')]

45 Page 116: destroy your left over samples HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY About 45 men and women 18 years of age and older will take part in this study HOW
60

[Li('Page 12: delayed The maximum study duration for Cohort 4 participants will be 48 weeks SAMPLE SIZE 60 evaluable participants approximately 15 evaluable participants in each cohort POPULATION HIV infected adults at least 18 '), Li('Page 88: criteria 9.4 Sample Size and Accrual The total sample size of this study will be 60 evaluable participants 12 evaluable active plus 3 evaluable placebo controls per dosing cohort if all four '), Li('Page 125: destroy your left over samples HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY About 60 men and women 18 years of age and older will take part in this study HOW '), Li('Page 134: destroy your left over blood HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY About 60 men and women 18 years of age and older will take part in this study about')]

Explanation: Number Of Arms

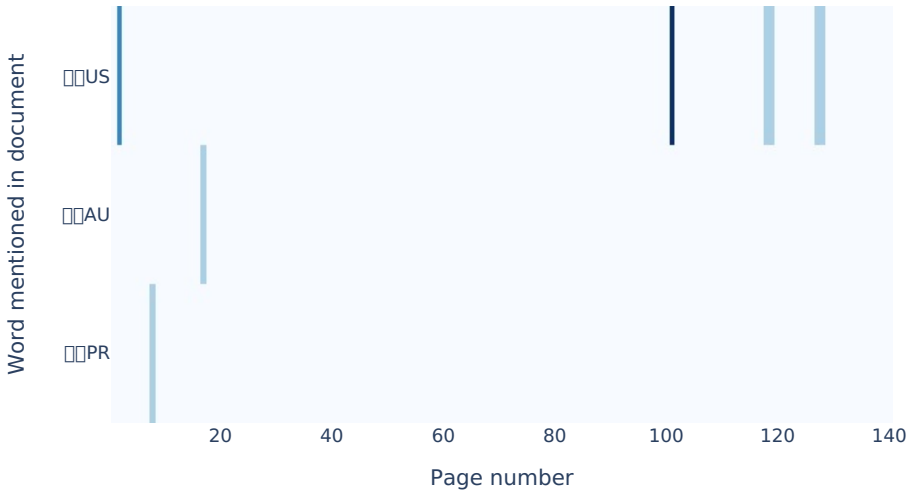
Which pages contained terms relating to the number of arms? The trial appears to have 3 arm(s).



Explanation: Country

Which countries were mentioned on which pages in the document? Estimated trial countries: **United States, one or more unspecified countries** . The AI looked at the countries which were mentioned more often and earlier on in the document than other countries. The graph below shows the candidate countries as a heat map throughout the pages of the document.

Graph of key COUNTRY related terms by page number in document



Possible mentions of COUNTRY in the document

United States

[Li('Page 2: and all applicable \n\nprotocol-related documents. I agree to conduct this study in compliance with United States (US) \n\nHealth and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug '), Li('Page 2: compliance with United States (US) \n\nHealth and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug \n\nAdministration regulations; standards of the International Conference on '), Li('Page 101: reservoir for \nHIV-1 in patients on highly active antiretroviral therapy. Proc Natl Acad Sci USA. \n1997;94:13193-7. \n\n5. Palmer S, Maldarelli F, Wiegand A, et al. Low-level viremia persists for '), Li('Page 101: for at least seven \nyears in patients on suppressive antiretroviral therapy. Proc Natl Acad Sci USA \n2008;105:3879-84. \n\n6. Dinoso JB, Kim SY, Wiegand AM, et al. Treatment intensification does not '), Li('Page 101: residual HIV-1 viremia in patients on highly active antiretroviral therapy. Proc Natl Acad \nSci USA 2009; 106 (23):9403-8. Epub 2009. \n\n7. McMahon D, Jones J, Wiegand A, et al. Raltegravir '), Li('Page 118: keep your personal information private, we have gotten a Certificate of Confidentiality \nfrom the U.S. Federal Government. This certificate means that researchers cannot be forced to \ntell people who '), Li('Page 119: . A description of this clinical trial will be available on ClinicalTrials.gov, as required by \nU.S. law. This website will not include information that can identify you. At most, the web site will '), Li('Page 127: keep your personal information private, we have gotten a Certificate of Confidentiality \nfrom the U.S. Federal Government. This certificate means that researchers cannot be forced to \ntell people who '), Li('Page 128: 128 A5315 \nFINAL Version 4.0 \n\n 06/07/18 \n\n \nU.S. law. This website will not include information that can identify you. At most, the web site will')]

Puerto Rico Page 8: : dragavon@u.washington.edu Carmen Irizarry, MT, (ASCP) Medical Science Campus University of Puerto Rico Pathology 606-A San Juan PR 00935 Phone: 787-758-5815 FAX: 787-751-9210 E-Mail: lab053.rcm@
Australia Page 17: administered daily for 14 days in HIV-infected participants with suppressed viremia in Australia has concluded and demonstrated an increase in HIV transcription from latency in the majority of

Explanation: Simulation

Which pages mentioned words related to simulation? The graph below shows a selection of simulation-related terms by page number. The protocol is 0.0% likely to involve simulation for sample size.