WEBVTT

1 00:00:00.870 --> 00:00:01.743 <v ->For this time.</v>

2 00:00:02.700 --> 00:00:03.533 So we're

3 00:00:03.533 --> 00:00:04.830 (presenter muttering indistinctly)

4 00:00:04.830 --> 00:00:07.620 <v ->All right, so hey, everybody, welcome.</v>

5 00:00:07.620 --> 00:00:11.010 Today's my privilege to introduce Dr. Glen Laird.

6 00:00:11.010 --> 00:00:13.200 Dr. Laird earned his PhD in statistics

7 00:00:13.200 --> 00:00:15.870 from Florida State University in 2000,

8 00:00:15.870 --> 00:00:17.460 then worked as a survey statistician

9 00:00:17.460 --> 00:00:20.160 for RTI International before joining

10 00:00:20.160 --> 00:00:22.200 the pharmaceutical industry

11 00:00:22.200 --> 00:00:23.670 where he worked at Novartis,

12 00:00:23.670 --> 00:00:27.050 Bristol Myers Squibb and Sanofi.

13 00:00:27.050 --> 00:00:30.603 And so now, he's at Vertex Pharmaceuticals.

14 00:00:31.440 --> 00:00:33.153 And so let's welcome Dr. Laird.

15 00:00:36.780 --> 00:00:41.070 <v ->I hope everybody can hear me also online.</v>

16 00:00:41.070 --> 00:00:43.156 I hope we can have a good discussion today.

17 00:00:43.156 --> 00:00:43.989 Have a lot to talk about.

18 00:00:43.989 --> 00:00:47.820 Feel free to interrupt me at any time with questions.

19 00:00:47.820 --> 00:00:50.700 There's really nothing overtly technical here,

20 00:00:50.700 --> 00:00:54.390 so I wanna be very accessible to everyone.

21 00:00:54.390 --> 00:00:57.660 I'd like to hear your feedback go along.

22 00:00:57.660 --> 00:00:59.550 So I'm gonna be talking today

23 00:00:59.550 --> 00:01:02.160 about industry-sponsored clinical trials,

24 00:01:02.160 --> 00:01:06.363 that is pharmaceutical industry sponsored trials.

25 00:01:08.250 --> 00:01:10.140 So disclaimer, I work for Vertex,

26 00:01:10.140 --> 00:01:12.603 but any opinions are mine, not theirs.

27 00:01:14.250 --> 00:01:16.233 So for a clinical trial,

28 00:01:17.742 --> 00:01:19.950 you're gonna have a clinical trial team, right?

29 00:01:19.950 --> 00:01:22.320 At Vertex, we call it a study execution team.

30 00:01:22.320 --> 00:01:24.120 Other companies call it something different,

31 00:01:24.120 --> 00:01:25.110 but it's the same kinda thing.

32 00:01:25.110 --> 00:01:27.900 It's a group of people who are responsible for running,

33 00:01:27.900 --> 00:01:29.523 conducting, executing the trial.

34 00:01:30.960 --> 00:01:32.100 It's gonna vary by the study,

35 00:01:32.100 --> 00:01:35.700 but usually, this is gonna include a clinician of course,

36 00:01:35.700 --> 00:01:39.210 who's gonna make the key clinical decisions about the study.

37 00:01:39.210 --> 00:01:42.273 An operations person's gonna do a lot of coordinating

38 00:01:42.273 --> 00:01:45.750 with the site, a lot of communication with the site

39 00:01:45.750 --> 00:01:47.610 actually conducting the study.

40 00:01:47.610 --> 00:01:50.370 Also shepherding documents through reviewing,

41 00:01:50.370 --> 00:01:51.690 things like that.

42 00:01:51.690 --> 00:01:55.110 Clinical pharmacology, they deal with pharmacokinetics,

43 00:01:55.110 --> 00:01:59.070 which is how the body processes the drug,

44 00:01:59.070 --> 00:02:00.693 metabolism, that sort of thing.

45 00:02:02.220 --> 00:02:03.420 Safety,

46 00:02:03.420 --> 00:02:06.840 at some point, FDA let it be known that they wanted you

47 00:02:06.840 --> 00:02:10.300 to have a person explicitly responsible for safety

48 00:02:11.649 --> 00:02:14.040 on your study team, so.

49 00:02:14.040 --> 00:02:15.960 Because then, I think there was kind of a mindset

50 00:02:15.960 --> 00:02:17.250 that if you had the same person

51 00:02:17.250 --> 00:02:21.360 trying to look at safety and efficacy,

52 00:02:21.360 --> 00:02:23.460 that they would probably end up spending most of their time

53 00:02:23.460 --> 00:02:24.960 looking at efficacy.

54 00:02:24.960 --> 00:02:26.910 Safety might not get the attention it deserves,

55 00:02:26.910 --> 00:02:30.360 so you have to have a person explicitly for safety.

56 00:02:30.360 --> 00:02:31.410 Clinical biomarkers,

57 00:02:31.410 --> 00:02:33.930 we often like to look at a lot of different biomarkers.

58 00:02:33.930 --> 00:02:38.280 Data management deals with the actual database itself,

59 00:02:38.280 --> 00:02:39.600 setting it up

60 00:02:39.600 --> 00:02:42.870 and the sort of execution around locking it

61 00:02:42.870 --> 00:02:43.800 and all that sort of thing.

62 00:02:43.800 --> 00:02:45.993 And cleaning the data.

63 00:02:47.940 --> 00:02:51.780 The statistical programmer is responsible for a lot

64 00:02:51.780 --> 00:02:55.950 of the actual execution of the various plans, right?

65 00:02:55.950 --> 00:02:57.900 So, and, of course, the statistician,

66 00:02:57.900 --> 00:03:00.600 which I'm gonna talk a little bit more about.

67 00:03:00.600 --> 00:03:01.920 The statistician and the programmer

68 00:03:01.920 --> 00:03:05.310 really work kinda hand in hand for a lot of things, right?

69 00:03:05.310 --> 00:03:07.410 There's a lot of things where the statistician

70 00:03:07.410 --> 00:03:09.297 is planning things, specifying things,

71 00:03:09.297 --> 00:03:12.150 and the programmer is the one writing the code

72 00:03:12.150 --> 00:03:13.923 to actually execute it.

73 00:03:18.240 --> 00:03:22.050 FYI, so what I just talked about was a study level team.

74 00:03:22.050 --> 00:03:23.880 There's also a project level team.

75 00:03:23.880 --> 00:03:27.510 So by project, I mean a drug or a therapy, right?

76 00:03:27.510 --> 00:03:29.610 So there'd be some more senior people.

77 00:03:29.610 --> 00:03:32.220 So there would be like a project level statistician

78 00:03:32.220 --> 00:03:33.960 and a team at the project level

79 00:03:33.960 --> 00:03:37.680 with a lot of these same similar functions plus some others.

80 00:03:37.680 --> 00:03:39.480 Legal, for example, comes to mind.

81 00:03:39.480 --> 00:03:41.550 That project team kinda guides

82 00:03:41.550 --> 00:03:44.520 the overall development of the drug.

83 00:03:44.520 --> 00:03:47.583 But today, I'm gonna focus more on the study,

84 00:03:50.610 --> 00:03:52.860 what the statistician and that team is doing.

85 00:03:53.820 --> 00:03:55.557 A lot of you may know this,

86 00:03:55.557 --> 00:03:59.050 but there's four sort of commonly recognized phases

87 00:04:00.353 --> 00:04:01.560 in drug development.

88 00:04:01.560 --> 00:04:04.020 Phase one is mostly about safety.

89 00:04:04.020 --> 00:04:07.290 You're trying to find the right dose of the drug.

90 00:04:07.290 --> 00:04:10.980 Phase two is kind of an initial assessment of efficacy,

91 00:04:10.980 --> 00:04:12.960 whether you think the drug works.

92 00:04:12.960 --> 00:04:15.630 Main purpose of that is to convince yourself

93 00:04:15.630 --> 00:04:17.790 whether you want to do phase three,

94 00:04:17.790 --> 00:04:21.330 which is the pivotal study,

95 00:04:21.330 --> 00:04:24.780 the main bulk of your evidence that you claim to submit,

96 00:04:24.780 --> 00:04:29.460 to say, "Here's our evidence that this drug works."

97 00:04:29.460 --> 00:04:33.180 Right, that study is often the biggest

98 00:04:33.180 --> 00:04:35.463 and it's generally randomized, right?

99 00:04:37.034 --> 00:04:37.867 And then there's phase four,

100 00:04:37.867 --> 00:04:40.301 which would be anything that's post

101 00:04:40.301 --> 00:04:41.160 (Glen muttering indistinctly)

102 00:04:41.160 --> 00:04:42.630 right, and those kinda studies

103 00:04:42.630 --> 00:04:45.780 can depend on the market conditions for your drug

104 00:04:45.780 --> 00:04:48.663 after it's gotten on the market.

105 00:04:49.590 --> 00:04:51.810 I'm gonna focus the most on the phase two,

106 00:04:51.810 --> 00:04:53.670 three type studies

107 00:04:53.670 --> 00:04:56.790 'cause that is sort of the most classic

108 00:04:56.790 --> 00:04:58.710 clinical trial experience.

109 00:04:58.710 --> 00:05:01.560 And it's perhaps the part where the statistician

110 00:05:01.560 --> 00:05:06.180 and the programmer are really the most key to being

111 00:05:06.180 --> 00:05:07.530 and their involvement.

112 00:05:07.530 --> 00:05:11.700 That is the scientific rigor of actually demonstrating

113 00:05:11.700 --> 00:05:13.263 this drug works.

114 00:05:17.010 --> 00:05:19.590 And as I noted the bottom there,

115 00:05:19.590 --> 00:05:21.720 the great majority of drugs that start in phase one

116 00:05:21.720 --> 00:05:25.740 end up dying somewhere along the way unfortunately.

117 00:05:25.740 --> 00:05:27.180 You can look up various numbers,

118 00:05:27.180 --> 00:05:30.000 but it's a pretty small percentage and actually end up

119 00:05:30.000 --> 00:05:32.460 making it to the market, unfortunately,

120 00:05:32.460 --> 00:05:34.160 from direct to start in phase one.

121 00:05:36.090 --> 00:05:36.923 Oh, okay.

122 00:05:36.923 --> 00:05:38.570 All right, so now we're at the survey here.

123 00:05:39.930 --> 00:05:42.170 All right, so all right, then.

124 00:05:42.170 --> 00:05:43.290 So then. <v ->Yep.</v>

125 00:05:43.290 --> 00:05:46.500 <v ->This is my survey question, hope everybody.</v>

126 00:05:46.500 --> 00:05:47.760 <v ->Oh, and then just hit present.</v>

127 00:05:47.760 --> 00:05:51.870 <v ->And then I need to do this,</v>

128 00:05:51.870 --> 00:05:52.913 so, okay.

129 00:05:54.930 --> 00:05:59.580 So I'm wondering what you think.

130 00:05:59.580 --> 00:06:04.580 So when in the life of a study do you think is the most work

131 00:06:05.280 --> 00:06:06.423 for the statistician?

132 00:06:07.560 --> 00:06:11.553 So if you can't see there, so option A,

133 00:06:12.420 --> 00:06:15.510 these plots are qualitative, it's conceptual, right?

134 00:06:15.510 --> 00:06:17.910 So the x-axis is time,

135 00:06:17.910 --> 00:06:19.830 the y-axis is the amount of work, right?

136 00:06:19.830 --> 00:06:23.370 So option A would be level, you know?

137 00:06:23.370 --> 00:06:25.680 It's basically the same amount of work over the whole course

138 00:06:25.680 --> 00:06:28.450 of the study from when you first start conceiving the study

139 00:06:28.450 --> 00:06:30.660 until you rep the study before, right?

140 00:06:30.660 --> 00:06:33.360 Option B is going up and up and up,

141 00:06:33.360 --> 00:06:34.800 getting busier and busier and busier

142 00:06:34.800 --> 00:06:36.720 the longer the study goes on.

143 00:06:36.720 --> 00:06:40.083 C is the opposite. Start very busy, gets less and less busy.

144 00:06:41.100 --> 00:06:46.100 D is Gaussian looking, right?

145 00:06:46.230 --> 00:06:48.330 There's a bulge of work in the middle.

146 00:06:48.330 --> 00:06:50.100 And E is kind of the opposite of that.

147 00:06:50.100 --> 00:06:52.410 A lot of work at the beginning and the end,

148 00:06:52.410 --> 00:06:53.510 maybe a bit of a lump.

149 00:06:55.770 --> 00:06:59.430 So I know people know how to fill this out or.

150 00:06:59.430 --> 00:07:00.360 <v ->Yep, text.</v>

151 00:07:00.360 --> 00:07:01.650 <v ->Whatever.</v> <v ->Get our your phones,</v>

152 00:07:01.650 --> 00:07:03.485 which you don't hear often.

153 00:07:03.485 --> 00:07:05.203 (Glen laughing)

154 00:07:05.203 --> 00:07:06.036 <v ->Yeah.</v>

155 00:07:14.040 --> 00:07:15.993 People online, I hope, are voting too.

156 00:07:20.340 --> 00:07:24.903 When do you think the most work is?

157 00:07:29.490 --> 00:07:33.633 Most people answered D.

158 00:07:35.371 --> 00:07:36.750 Maybe I don't know how to tell how many people,

159 00:07:36.750 --> 00:07:38.971 I hope it's more than. <v ->Yeah. (laughs)</v>

160 00:07:38.971 --> 00:07:41.483 <v ->I hope it's more than like six people that are voting.</v>

161 00:07:42.720 --> 00:07:44.610 I feel good when you see some prime numbers

162 00:07:44.610 --> 00:07:47.039 and stuff in there, it makes you feel like,

163 00:07:47.039 --> 00:07:48.873 "Okay, 10 must be big enough

164 00:07:48.873 --> 00:07:50.070 that you're getting something."

165 00:07:50.070 --> 00:07:54.600 But, okay, so it looks like most people say D,

166 00:07:54.600 --> 00:07:57.210 fair number of people say E,

167 00:07:57.210 --> 00:07:59.310 now, it's not a lot for the other choices.

168 00:08:01.260 --> 00:08:02.640 Like so do I just go back?

169 00:08:02.640 --> 00:08:04.292 And how do I go back? <v ->Yeah, you just go back</v>

170 00:08:04.292 --> 00:08:05.125 to that.

171 00:08:05.125 --> 00:08:07.163 <v ->Do I just hit escape?</v> <v ->Escape. Yeah, you can.</v>

172 00:08:12.240 --> 00:08:13.143 <v ->Present mode.</v>

173 00:08:15.570 --> 00:08:16.520 <v ->It's not working?</v>

174 00:08:18.510 --> 00:08:19.560 <v ->That's it?</v> <v ->Yeah.</v>

175 00:08:20.399 --> 00:08:22.013 <v ->I think we're out of present mode though.</v>

176 00:08:23.970 --> 00:08:25.720 <v ->Yeah.</v> <v ->There we go.</v>

177 00:08:25.720 --> 00:08:27.750 <v ->So in my opinion, I think most people</v>

178 00:08:27.750 --> 00:08:28.920 would agree with this.

179 00:08:28.920 --> 00:08:30.770 I would say the answer is actually E,

180 00:08:32.430 --> 00:08:34.860 the opposite of what most of you picked.

181 00:08:34.860 --> 00:08:37.170 And the reason for that is there's a lot of stuff

182 00:08:37.170 --> 00:08:39.330 the statistician has to do at the beginning of the study

183 00:08:39.330 --> 00:08:40.770 in terms of planning,

184 00:08:40.770 --> 00:08:43.680 specifying what kinda study are we gonna do,

185 00:08:43.680 --> 00:08:45.180 how are we gonna plan all kinds of stuff.

186 00:08:45.180 --> 00:08:47.850 I'll talk some more detail in just a minute.

187 00:08:47.850 --> 00:08:49.290 And then there's a lot of work reporting

188 00:08:49.290 --> 00:08:50.880 at the end of the study

189 00:08:50.880 --> 00:08:53.820 executing everything you said you were gonna do, right?

190 00:08:53.820 --> 00:08:56.077 And it's not uncommon that in the middle

191 00:08:56.077 --> 00:08:57.330 maybe there's a bit of a low

192 00:08:57.330 --> 00:08:59.970 where you're mostly kinda waiting for patients to enroll

193 00:08:59.970 --> 00:09:02.730 and everything is maybe blinded even.

194 00:09:02.730 --> 00:09:04.630 So you don't have it available, right?

195 00:09:05.610 --> 00:09:09.720 So what does the life of a study look like

196 00:09:09.720 --> 00:09:12.453 and what is the statistician doing during this study?

197 00:09:15.246 --> 00:09:16.920 So I'm gonna give you an outline.

198 00:09:16.920 --> 00:09:19.410 Again, it's just main steps.

199 00:09:19.410 --> 00:09:21.210 Don't take anything here too literally,

200 00:09:21.210 --> 00:09:24.030 this is just kind of my ballparking of things,

201 00:09:24.030 --> 00:09:26.643 way things tend to go at most companies,

202 00:09:27.690 --> 00:09:30.210 but companies in general are more alike than different.

203 00:09:30.210 --> 00:09:33.060 A lot of this process is actually quite standard.

204 00:09:33.060 --> 00:09:35.460 They just have little different flavors, you know,

205 00:09:35.460 --> 00:09:37.410 different tweaking of the timelines and such.

206 00:09:37.410 --> 00:09:40.920 But the general idea should be pretty consistent.

207 00:09:40.920 --> 00:09:44.520 This isn't covering special studies, targeted study.

208 00:09:44.520 --> 00:09:46.800 I'm talking about a sort of a classic, you know,

209 00:09:46.800 --> 00:09:49.341 phase three type study here.

210 00:09:49.341 --> 00:09:50.423 <v ->You wanna move that window?</v>

211 00:09:51.819 --> 00:09:53.062 <v ->Yes.</v>

212 00:09:53.062 --> 00:09:54.062 <v ->I'm sorry.</v>

213 00:09:55.014 --> 00:09:56.520 <v ->Thank you 'cause I've got that.</v>

214 00:09:56.520 --> 00:09:57.353 <v ->I know it's hard to figure out.</v>

215 00:09:57.353 --> 00:09:59.375 <v ->Stuff I want to, yeah.</v>

216 00:09:59.375 --> 00:10:00.660 So the first thing you notice here

217 00:10:00.660 --> 00:10:03.060 is that there's tons of acronyms, right?

218 00:10:03.060 --> 00:10:05.520 That's part and parcel in the industry.

219 00:10:05.520 --> 00:10:06.770 There's a lot of things here.

220 00:10:06.770 --> 00:10:07.890 But that right, I'll go through 'em.

221 00:10:07.890 --> 00:10:11.310 So the first thing here starts with protocol concept, right?

222 00:10:11.310 --> 00:10:13.650 So the protocol concept is basically a document

223 00:10:13.650 --> 00:10:15.330 that just gives you kinda the bare bones

224 00:10:15.330 --> 00:10:18.030 of what do you plan to do in this study?

225 00:10:18.030 --> 00:10:19.140 What's the disease?

226 00:10:19.140 --> 00:10:21.240 What kinda patients do you plan to enroll?

227 00:10:21.240 --> 00:10:23.160 What are you gonna measure on those patients?

228 00:10:23.160 --> 00:10:24.660 When are you gonna measure it?

229 00:10:25.950 --> 00:10:28.269 A little bit about how you're gonna analyze it.

230 00:10:28.269 --> 00:10:29.550 And, of course, the sample size, right?

231 00:10:29.550 --> 00:10:33.660 Which the statistician has to calculate

232 00:10:33.660 --> 00:10:35.820 how many patients you're gonna study, right?

233 00:10:35.820 --> 00:10:37.800 That gets reviewed by various functions,

234 00:10:37.800 --> 00:10:39.870 including, of course, biostats.

235 00:10:39.870 --> 00:10:43.110 And also gets reviewed by a PRC,

236 00:10:43.110 --> 00:10:45.513 which is a protocol review committee.

237 00:10:46.890 --> 00:10:48.600 And oh, they got blocked out a bit there.

238 00:10:48.600 --> 00:10:53.010 So FSFV is first subject, first visit.

239 00:10:53.010 --> 00:10:54.090 If you're studying patients,

240 00:10:54.090 --> 00:10:56.130 you often say first patient first visit.

241 00:10:56.130 --> 00:10:57.810 So those are really the same thing,

242 00:10:57.810 --> 00:11:00.570 just depending on whether you're actually studying patients

243 00:11:00.570 --> 00:11:01.620 that have the disease

244 00:11:01.620 --> 00:11:04.173 or just healthy volunteers for example.

245 00:11:06.030 --> 00:11:10.200 And so this gets reviewed by the protocol review committee.

246 00:11:10.200 --> 00:11:11.640 Again, that's one of those things

247 00:11:11.640 --> 00:11:13.890 that every company's gonna have

248 00:11:13.890 --> 00:11:15.990 one or more protocol review committees,

249 00:11:15.990 --> 00:11:17.400 but they're all gonna be,

250 00:11:17.400 --> 00:11:18.990 and they're gonna have a little different flavor,

251 00:11:18.990 --> 00:11:21.240 but it's gonna be pretty similar.

252 00:11:21.240 --> 00:11:23.460 So if it's approved by the PRC,

253 00:11:23.460 --> 00:11:26.730 then you come back maybe two, three months later, say,

254 00:11:26.730 --> 00:11:27.963 with a full protocol,

255 00:11:28.890 --> 00:11:32.610 which should be very similar to the protocol concept.

256 00:11:32.610 --> 00:11:34.067 You're just filling in more details

257 00:11:34.067 --> 00:11:37.143 of how are you gonna measure these endpoints, for example.

258 00:11:38.010 --> 00:11:41.280 You know, details on inclusion and exclusion criteria

259 00:11:41.280 --> 00:11:44.310 for exactly who gets in the study, some things like that.

260 00:11:44.310 --> 00:11:47.520 Still doesn't have all the statistical

261 00:11:47.520 --> 00:11:49.320 details in it, right?

262 00:11:49.320 --> 00:11:50.670 Has some high-level summaries

263 00:11:50.670 --> 00:11:53.100 of what kind of analysis you plan to do.

264 00:11:53.100 --> 00:11:54.960 But it's not table shells,

265 00:11:54.960 --> 00:11:58.053 it's not the real statistical rigor details.

266 00:11:59.190 --> 00:12:01.470 So let's say that gets approved by the PRC.

267 00:12:01.470 --> 00:12:05.250 Now I move on to case report forms or CRFs.

268 00:12:05.250 --> 00:12:06.690 Those are the actual forms

269 00:12:06.690 --> 00:12:09.270 where the site enters the data, right?

270 00:12:09.270 --> 00:12:13.080 So principle here is the sites enter the data,

271 00:12:13.080 --> 00:12:16.620 the sites change the data, we don't touch the data, right?

272 00:12:16.620 --> 00:12:18.000 We just talk to them

273 00:12:18.000 --> 00:12:19.950 about how they're supposed to do that, right?

274 00:12:19.950 --> 00:12:21.697 We don't touch it, we just query them and say,

275 00:12:21.697 --> 00:12:24.870 "Hey, do you need to change this data?"

276 00:12:24.870 --> 00:12:27.210 And then it's up to them to change it.

277 00:12:27.210 --> 00:12:29.850 So it's important, this is a process

278 00:12:29.850 --> 00:12:32.190 not driven by biostatistics, right?

279 00:12:32.190 --> 00:12:35.400 Operations and data management, run it,

280 00:12:35.400 --> 00:12:38.460 but it's important for the statistician to be there

281 00:12:38.460 --> 00:12:43.140 and the programmer to review it and look, right?

282 00:12:43.140 --> 00:12:45.240 Because if you don't have a good case report form,

283 00:12:45.240 --> 00:12:47.280 you're not gonna get the data you need, right?

284 00:12:47.280 --> 00:12:49.830 You're gonna be in a bind at the end of the study

285 00:12:49.830 --> 00:12:51.570 when it turns out the form didn't collect

286 00:12:51.570 --> 00:12:53.313 what you wanted to report.

287 00:12:55.440 --> 00:12:57.000 Similar to that, there's edit checks.

288 00:12:57.000 --> 00:13:01.170 So edit checks is something to respond to the site

289 00:13:01.170 --> 00:13:04.050 whenever they enter something that is questionable, right?

290 00:13:04.050 --> 00:13:07.020 So the site enters that the patient was 200 years old,

291 00:13:07.020 --> 00:13:08.430 that's gotta be some kinda typo.

292 00:13:08.430 --> 00:13:11.107 It's gonna immediately spit up something saying,

293 00:13:11.107 --> 00:13:13.650 "Hey, double check that number, right?"

294 00:13:13.650 --> 00:13:17.160 So edit checks are important in terms of getting good data

295 00:13:17.160 --> 00:13:19.533 in the system in the first place, right?

296 00:13:21.000 --> 00:13:24.693 PD specifications. So PD stands for protocol deviation.

297 00:13:25.560 --> 00:13:27.360 In the real world,

298 00:13:27.360 --> 00:13:29.700 things don't always go according to the protocol, right?

299 00:13:29.700 --> 00:13:32.880 There's often missed assessments,

300 00:13:32.880 --> 00:13:36.180 assessments that weren't done at the right time.

301 00:13:36.180 --> 00:13:38.910 Patients that were enrolled that actually weren't supposed

302 00:13:38.910 --> 00:13:41.640 to be enrolled according to the infusion criteria,

303 00:13:41.640 --> 00:13:43.740 various things in the real world may go wrong.

304 00:13:43.740 --> 00:13:47.490 And so the statistician plays a key part in specifying

305 00:13:47.490 --> 00:13:49.560 what you're going to do about those, right?

306 00:13:49.560 --> 00:13:51.000 So this is still at the beginning, right?

307 00:13:51.000 --> 00:13:53.400 This is before you've enrolled anybody.

308 00:13:53.400 --> 00:13:57.990 You're planning, okay, we can foresee that this may happen.

309 00:13:57.990 --> 00:13:59.037 What are we gonna do about it?

310 00:13:59.037 --> 00:14:00.270 You might have a,

311 00:14:00.270 --> 00:14:03.030 you might say, if patients are not enrolled,

312 00:14:03.030 --> 00:14:03.900 if patients are enrolled

313 00:14:03.900 --> 00:14:07.110 who don't have the treatment history we intended,

314 00:14:07.110 --> 00:14:08.377 then, for example, you might say,

315 00:14:08.377 --> 00:14:09.390 "We're not gonna include that.

316 00:14:09.390 --> 00:14:10.950 We're not going to include that patient

317 00:14:10.950 --> 00:14:12.630 in this particular analysis."

318 00:14:12.630 --> 00:14:14.890 Might be one thing you would pre-specify

319 00:14:14.890 --> 00:14:16.200 about how are you gonna handle

320 00:14:16.200 --> 00:14:17.763 that protocol deviation, right?

321 00:14:20.040 --> 00:14:21.330 The randomization request.

322 00:14:21.330 --> 00:14:22.710 Every company's gonna have a form

323 00:14:22.710 --> 00:14:24.157 the status session fills out to say,

324 00:14:24.157 --> 00:14:26.610 "Please do the randomization in this way."

325 00:14:26.610 --> 00:14:28.260 We almost always do some form

326 00:14:28.260 --> 00:14:30.720 of stratify block randomization, right?

327 00:14:30.720 --> 00:14:33.600 So anybody who maybe doesn't know, right?

328 00:14:33.600 --> 00:14:37.530 A block is a small sample size where you know

329 00:14:37.530 --> 00:14:39.900 the randomization's gonna work out even, right?

330 00:14:39.900 --> 00:14:42.060 So if your block size is four,

331 00:14:42.060 --> 00:14:43.800 you're guaranteed that two of those four

332 00:14:43.800 --> 00:14:44.760 are gonna be treatment,

333 00:14:44.760 --> 00:14:46.890 two of those four are gonna be controlled, right?

334 00:14:46.890 --> 00:14:51.750 It's just a matter of which two bits the order.

335 00:14:51.750 --> 00:14:53.850 So that helps enforce some balance, right?

336 00:14:53.850 --> 00:14:57.120 And then we're gonna have stratification factors.

337 00:14:57.120 --> 00:15:01.320 Those are often a common topic for discussion

338 00:15:01.320 --> 00:15:03.280 and exactly what are we gonna stratify

339 00:15:04.380 --> 00:15:05.910 for the randomization, right?

340 00:15:05.910 --> 00:15:09.960 So a statistician's very important in making sure

341 00:15:09.960 --> 00:15:12.570 and figuring out how that randomization is gonna be done

342 00:15:12.570 --> 00:15:15.423 and filling out the form properly, right?

343 00:15:16.590 --> 00:15:18.270 The data monitoring plan,

344 00:15:18.270 --> 00:15:21.330 that's more driven by data management,

345 00:15:21.330 --> 00:15:24.390 but the statistician needs to look at it.

346 00:15:24.390 --> 00:15:25.650 So the monitoring plan is like

347 00:15:25.650 --> 00:15:28.470 how are we gonna look at the data in an ongoing way

348 00:15:28.470 --> 00:15:30.390 during the study, right?

349 00:15:30.390 --> 00:15:34.170 So if say sites are not understanding the protocol,

350 00:15:34.170 --> 00:15:35.940 they're enrolling the wrong kind of patients,

351 00:15:35.940 --> 00:15:38.520 you wanna catch it as soon as possible, right?

352 00:15:38.520 --> 00:15:41.760 So you're looking at baseline data, blinded data,

353 00:15:41.760 --> 00:15:44.580 and trying to see if there's problems that could affect

354 00:15:44.580 --> 00:15:47.223 the scientific validity of the study.

355 00:15:51.330 --> 00:15:53.193 Okay, then just,

356 00:15:58.530 --> 00:15:59.363 there we go.

357 00:15:59.363 --> 00:16:01.050 All right, so during the study,

358 00:16:01.050 --> 00:16:04.950 I have the red box here around finalize the SAP,

359 00:16:04.950 --> 00:16:08.550 which is the statistical analysis plan.

360 00:16:08.550 --> 00:16:11.190 This is the single document that the statistician

361 00:16:11.190 --> 00:16:13.140 is most responsible for.

362 00:16:13.140 --> 00:16:17.040 And that's the document, statistician authors it,

363 00:16:17.040 --> 00:16:19.890 facilitates the review of that document.

364 00:16:19.890 --> 00:16:23.610 This is the document where you do put all those details,

365 00:16:23.610 --> 00:16:25.590 all the statistical nitty gritty details

366 00:16:25.590 --> 00:16:28.050 about how are you gonna handle missing data?

367 00:16:28.050 --> 00:16:30.900 How exactly are you gonna define the baseline?

368 00:16:30.900 --> 00:16:31.740 What are you gonna do?

369 00:16:31.740 --> 00:16:34.380 What covariance are you gonna put in your model?

370 00:16:34.380 --> 00:16:37.740 All these kind of details about exactly how you plan

371 00:16:37.740 --> 00:16:39.747 to do the analysis, right?

372 00:16:39.747 --> 00:16:42.930 And this also gets reviewed and approved

373 00:16:42.930 --> 00:16:47.930 by all the usual review machinery in the company, right?

374 00:16:48.060 --> 00:16:50.730 So notice about the timing.

375 00:16:50.730 --> 00:16:54.960 So if you have a unblinded study,

376 00:16:54.960 --> 00:16:58.380 you need to do this before you enroll anybody, right?

377 00:16:58.380 --> 00:17:00.080 Before first patient, first visit.

378 00:17:01.710 --> 00:17:03.750 If you have a blinded study,

379 00:17:03.750 --> 00:17:05.410 it can be done somewhat later

380 00:17:06.630 --> 00:17:08.790 after you've started enrolling patients.

381 00:17:08.790 --> 00:17:11.650 You still need to do it in time to allow programming

382 00:17:12.557 --> 00:17:15.450 to do the programming and validate stuff and all that.

383 00:17:15.450 --> 00:17:17.100 You can't do it at the last minute,

384 00:17:17.100 --> 00:17:20.430 but you don't have to do it before you enroll a patient.

385 00:17:20.430 --> 00:17:24.750 Does anybody have any idea why that would matter?

386 00:17:24.750 --> 00:17:27.300 Whether it's a blinded study or not on the timings?

387 00:17:32.190 --> 00:17:34.386 Somebody who doesn't have sandwich in their mouth, perhaps.

388 00:17:34.386 --> 00:17:36.196 (attendant chuckling)

389 00:17:36.196 --> 00:17:37.446 <v ->You have the big rooms.</v>

390 00:17:42.930 --> 00:17:45.690 <v ->I highlight this because this is another</v>

391 00:17:45.690 --> 00:17:48.300 very important principle of these studies,

392 00:17:48.300 --> 00:17:51.183 which is pre-specification, right?

393 00:17:52.080 --> 00:17:56.460 Things that you say and do after the data are known,

394 00:17:56.460 --> 00:17:58.710 after you know who's and what treatment group

395 00:17:58.710 --> 00:18:02.100 are considered post hoc, right?

396 00:18:02.100 --> 00:18:03.948 And they're going to be viewed,

397 00:18:03.948 --> 00:18:05.760 I'm not sure if suspiciously is quite the right word,

398 00:18:05.760 --> 00:18:10.230 but are gonna be viewed with additional skepticism, right?

399 00:18:10.230 --> 00:18:13.560 So before that, you start enrolling patients,

400 00:18:13.560 --> 00:18:15.300 or before the study's unblinded,

401 00:18:15.300 --> 00:18:18.240 you can still claim that you're pre-specifying things.

402 00:18:18.240 --> 00:18:20.550 Hey, when I said we were gonna do the analysis this way,

403 00:18:20.550 --> 00:18:22.860 I didn't know that this patient was in treatment

404 00:18:22.860 --> 00:18:25.110 and that patient was controlled, right?

405 00:18:25.110 --> 00:18:27.490 So you could still claim to be even handed

406 00:18:28.620 --> 00:18:30.480 when you do the plan.

407 00:18:30.480 --> 00:18:33.210 Then I'd say maybe comes the lull

408 00:18:33.210 --> 00:18:36.030 I was talking about, right?

409 00:18:36.030 --> 00:18:38.310 Maybe in the middle, yes, you're executing the data,

410 00:18:38.310 --> 00:18:40.980 monitoring stuff that you said you were gonna plan.

411 00:18:40.980 --> 00:18:44.703 That's not really heavily driven by stats.

412 00:18:45.810 --> 00:18:48.450 There's always gonna be team meetings.

413 00:18:48.450 --> 00:18:50.100 It varies, they might be say monthly.

414 00:18:50.100 --> 00:18:54.450 A lot of that is kind of study status things on enrollment

415 00:18:54.450 --> 00:18:57.000 and discussions about whether we need to do an amendment

416 00:18:57.000 --> 00:18:58.110 to the study.

417 00:18:58.110 --> 00:19:00.150 Again, not really driven by stats, right?

418 00:19:00.150 --> 00:19:02.100 So maybe there's a bit of a lull there.

419 00:19:02.100 --> 00:19:03.450 Then as you're starting to get closer

420 00:19:03.450 --> 00:19:06.630 towards clinical database lock,

421 00:19:06.630 --> 00:19:08.790 which is what CDBL is, right?

422 00:19:08.790 --> 00:19:10.620 Now, you want to do dry runs.

423 00:19:10.620 --> 00:19:13.750 So by now, programming has done the programs

424 00:19:15.120 --> 00:19:19.890 you want to execute those programs on some version

425 00:19:19.890 --> 00:19:23.610 of the data in order to see whether there's, you know,

426 00:19:23.610 --> 00:19:25.170 issues at the tables look fine.

427 00:19:25.170 --> 00:19:27.940 So a lot of times when people do the blinded study

428 00:19:29.040 --> 00:19:31.470 is you're gonna use dummy codes,

429 00:19:31.470 --> 00:19:35.220 you just make up false treatment assignments

430 00:19:35.220 --> 00:19:37.140 and you stick that in and then you run the table

431 00:19:37.140 --> 00:19:39.240 and you just kinda see where they're fine.

432 00:19:40.650 --> 00:19:44.550 Then you have to identify the protocol deviations.

433 00:19:44.550 --> 00:19:46.020 This is the part where,

434 00:19:46.020 --> 00:19:47.910 remember earlier you were planning

435 00:19:47.910 --> 00:19:49.920 how you're gonna handle the deviations.

436 00:19:49.920 --> 00:19:52.333 Now you can get close to database lock,

437 00:19:52.333 --> 00:19:54.300 you have to execute that.

438 00:19:54.300 --> 00:19:56.257 You have to apply it to the actual data and say,

439 00:19:56.257 --> 00:19:58.080 "Hey, just looking at the baseline data,

440 00:19:58.080 --> 00:20:00.450 I still don't know who's treatment, who's control."

441 00:20:00.450 --> 00:20:03.930 I'm gonna say that patient is not in that analysis

442 00:20:03.930 --> 00:20:06.360 because of the rule I said before

443 00:20:06.360 --> 00:20:09.480 and I'm doing this now before I know, right?

444 00:20:09.480 --> 00:20:11.130 So you have to do that kind of applying it

445 00:20:11.130 --> 00:20:12.697 and you have to sign off on that saying,

446 00:20:12.697 --> 00:20:15.837 "Here's the official call of who had what deviation."

447 00:20:18.030 --> 00:20:21.360 Then at the database lock, there's all the reporting stuff.

448 00:20:21.360 --> 00:20:23.553 You fill out a form to unblind the data.

449 00:20:24.720 --> 00:20:27.060 Usually very quickly, within a week or two,

450 00:20:27.060 --> 00:20:29.520 you have to deliver the key results.

451 00:20:29.520 --> 00:20:32.910 Vertex would call it the key reports memo or KRM,

452 00:20:32.910 --> 00:20:35.190 other companies call it something similar.

453 00:20:35.190 --> 00:20:37.140 But basically, within a week or two,

454 00:20:37.140 --> 00:20:40.343 management's gonna wanna know kinda the bottom line, right?

455 00:20:40.343 --> 00:20:43.020 And was the p-value less than 0.05?

456 00:20:43.020 --> 00:20:45.420 Was there some kinda major safety situation

457 00:20:45.420 --> 00:20:46.980 we oughta be aware of?

458 00:20:46.980 --> 00:20:48.300 That kinda thing, right?

459 00:20:48.300 --> 00:20:51.750 After that come the full list of tables,

460 00:20:51.750 --> 00:20:53.250 listings and figures.

461 00:20:53.250 --> 00:20:54.300 And then you have to finalize

462 00:20:54.300 --> 00:20:56.260 the clinical study report for CSR.

463 00:20:57.747 --> 00:21:00.840 And for that, you would have to author, you know,

464 00:21:00.840 --> 00:21:02.807 the statistical section of CSR.

465 00:21:04.080 --> 00:21:07.859 So that is kind of an overview of this is what a clinical,

466 00:21:07.859 --> 00:21:10.380 you know, study sort of looks like to a statistician

467 00:21:10.380 --> 00:21:11.883 and how you're doing, right?

468 00:21:16.890 --> 00:21:20.100 I'll note that it does vary some by the phase, right?

469 00:21:20.100 --> 00:21:24.030 To me, phase one, it's more exploratory.

470 00:21:24.030 --> 00:21:25.530 It's often unblinded.

471 00:21:25.530 --> 00:21:27.167 There's more kinda going on during the study

472 00:21:27.167 --> 00:21:29.970 'cause you don't really understand the drug yet, right?

473 00:21:29.970 --> 00:21:32.910 So there's amendments maybe more common,

474 00:21:32.910 --> 00:21:34.380 I think of it a little bit

475 00:21:34.380 --> 00:21:36.737 more like drug babysitting, you know?

476 00:21:36.737 --> 00:21:39.990 You're kinda like, "Okay, what's gonna happen today,

477 00:21:39.990 --> 00:21:41.850 you know, with each new dose that's going on?"

478 00:21:41.850 --> 00:21:46.380 So there's kinda more work to do during the study.

479 00:21:46.380 --> 00:21:48.570 People don't worry as much about the planning

480 00:21:48.570 --> 00:21:51.720 'cause everybody knows it's exploratory, right?

481 00:21:51.720 --> 00:21:53.280 Phase three is kinda the opposite.

482 00:21:53.280 --> 00:21:57.990 Everything I just said before, lots of planning, you know?

483 00:21:57.990 --> 00:22:00.180 Lots of trying to pre-specify things.

484 00:22:00.180 --> 00:22:02.430 Even things that are maybe somewhat unlikely,

485 00:22:03.540 --> 00:22:05.850 you know, very rigorous, right?

486 00:22:05.850 --> 00:22:07.680 It's 'cause it's often a very big study,

487 00:22:07.680 --> 00:22:09.993 it's very expensive, it's very costly,

488 00:22:11.010 --> 00:22:14.270 and a number of ways, if it fails, it's gonna be, you know,

489 00:22:14.270 --> 00:22:16.500 it could be pretty bad for the company

490 00:22:16.500 --> 00:22:18.450 depending on the situation, right?

491 00:22:18.450 --> 00:22:20.940 But the point is you have to carefully consider,

492 00:22:20.940 --> 00:22:22.383 you know, the details.

493 00:22:23.310 --> 00:22:25.770 There's more attention, more review by both management

494 00:22:25.770 --> 00:22:27.893 and, of course, health authorities like FDA.

495 00:22:31.320 --> 00:22:33.300 So for phase four,

496 00:22:33.300 --> 00:22:37.830 there's a group often called Global Medical Affairs.

497 00:22:37.830 --> 00:22:40.140 There's another group called Health Economics

498 00:22:40.140 --> 00:22:42.540 that often deal with these kind of studies.

499 00:22:42.540 --> 00:22:45.873 You can often look at longer-term safety and efficacy.

500 00:22:47.340 --> 00:22:49.233 They may address reimbursement.

501 00:22:50.190 --> 00:22:53.400 So reimbursement is kind of a bigger deal in Europe

502 00:22:53.400 --> 00:22:56.580 because they have single-payer systems.

503 00:22:56.580 --> 00:23:01.050 And so just because you get a drug approved by the EMA,

504 00:23:01.050 --> 00:23:03.240 which is kinda their version of FDA,

505 00:23:03.240 --> 00:23:04.380 that means you can sell it,

506 00:23:04.380 --> 00:23:05.213 but that doesn't mean

507 00:23:05.213 --> 00:23:06.900 the governments have to pay for it, right?

508 00:23:06.900 --> 00:23:09.727 You have to make a separate case to them to say,

509 00:23:09.727 --> 00:23:13.380 ”Hey, not only does this drug work,

510 00:23:13.380 --> 00:23:16.680 it's actually worth what we want you to pay for, right?”

511 00:23:16.680 --> 00:23:18.730 There's a negotiation there.

512 00:23:18.730 --> 00:23:22.050 There gonna be a lot of publications involved in this.

513 00:23:22.050 --> 00:23:24.330 I don't know if you've heard the term real-world evidence

514 00:23:24.330 --> 00:23:25.350 or real-world data,

515 00:23:25.350 --> 00:23:29.070 but this is being used more and more in phase four.

516 00:23:29.070 --> 00:23:33.000 Once the drug is on the market in the real world,

517 00:23:33.000 --> 00:23:35.130 there's data related to that.

518 00:23:35.130 --> 00:23:38.010 There's insurance claims,

519 00:23:38.010 --> 00:23:40.200 there's electronic health records,

520 00:23:40.200 --> 00:23:43.740 things that weren't around back when I started, right?

521 00:23:43.740 --> 00:23:46.790 That can help you understand what's going on

522 00:23:46.790 --> 00:23:48.237 in the real world with your drug.

523 00:23:48.237 --> 00:23:50.100 And these are often very big datasets,

524 00:23:50.100 --> 00:23:53.310 but they can also be kind of messy in a lot of ways.

525 00:23:53.310 --> 00:23:58.080 Sometimes, there's a specific group for real-world evidence,

526 00:23:58.080 --> 00:24:02.190 but sometimes, that group is closely aligned biostats.

527 00:24:02.190 --> 00:24:04.229 Vertex has a group called

528 00:24:04.229 --> 00:24:05.062 (Glen muttering indistinctly)

529 00:24:05.062 --> 00:24:05.895 statistics,

530 00:24:05.895 --> 00:24:08.880 which is statisticians who are kind of particularly

531 00:24:08.880 --> 00:24:11.480 knowledgeable about dealing with these kind of data.

532 00:24:12.630 --> 00:24:13.567 People sometimes ask,

533 00:24:13.567 --> 00:24:16.140 "Well, what kinda statistics do you use?"

534 00:24:16.140 --> 00:24:18.120 Not really a good answer to that.

535 00:24:18.120 --> 00:24:21.300 It varies a lot by the disease you're using,

536 00:24:21.300 --> 00:24:23.220 by endpoint, I mean, variable,

537 00:24:23.220 --> 00:24:25.920 the outcome that you're measuring there.

538 00:24:25.920 --> 00:24:28.863 So it depends on the challenges of the setting.

539 00:24:30.930 --> 00:24:34.230 Like maybe sample size is a big issue,

540 00:24:34.230 --> 00:24:36.900 others may be missing data as a big problem.

541 00:24:36.900 --> 00:24:39.600 I used to work in oncology before I worked at Vertex.

542 00:24:39.600 --> 00:24:42.300 They use a lot of time to event endpoints,

543 00:24:42.300 --> 00:24:44.370 like time until the disease progresses.

544 00:24:44.370 --> 00:24:47.580 So they do a lot of survival analyses, right?

545 00:24:47.580 --> 00:24:49.770 Vertex, we don't do oncology anymore,

546 00:24:49.770 --> 00:24:53.340 so we have some time to event endpoints,

547 00:24:53.340 --> 00:24:54.480 but not that much.

548 00:24:54.480 --> 00:24:56.220 So the point is it just kinda depends

549 00:24:56.220 --> 00:24:57.990 on what you're studying.

550 00:24:57.990 --> 00:25:00.540 But, you know, companies understand that, you know,

551 00:25:01.380 --> 00:25:03.000 people aren't gonna necessarily walk in the door

552 00:25:03.000 --> 00:25:06.720 happening to be specialists in the exact kinda statistics

553 00:25:06.720 --> 00:25:08.880 that we're using right now.

554 00:25:08.880 --> 00:25:13.530 So, as an example of it depends on the setting.

555 00:25:13.530 --> 00:25:15.420 Vertex does a good bit in rare diseases.

556 00:25:15.420 --> 00:25:17.130 So I thought I'd just highlight a couple things

557 00:25:17.130 --> 00:25:18.510 about rare diseases.

558 00:25:18.510 --> 00:25:20.400 I'm not gonna go through all of these,

559 00:25:20.400 --> 00:25:21.810 but just in general,

560 00:25:21.810 --> 00:25:25.341 kind of the understanding of the disease and rare diseases

561 00:25:25.341 --> 00:25:26.174 can be limited.

562 00:25:27.090 --> 00:25:28.680 There haven't been a lot of studies

563 00:25:28.680 --> 00:25:30.060 conducted on this before.

564 00:25:30.060 --> 00:25:33.150 There's often not a lot of good prior information.

565 00:25:33.150 --> 00:25:36.243 Identifying patients can be difficult.

566 00:25:37.200 --> 00:25:38.970 You don't often get enough small sample sizes

567 00:25:38.970 --> 00:25:41.303 because there's not a lot of patients out there.

568 00:25:42.450 --> 00:25:46.590 A lot of these diseases are congenital, right?

569 00:25:46.590 --> 00:25:48.570 They're genetic, you're born with 'em.

570 00:25:48.570 --> 00:25:50.670 So a lot of the patients, I've read more than 1/2,

571 00:25:50.670 --> 00:25:51.870 are actually children.

572 00:25:51.870 --> 00:25:54.870 So, you know, that creates a whole nother aspect

573 00:25:54.870 --> 00:25:58.473 to the study if you're trying to study this in a child.

574 00:25:59.670 --> 00:26:02.940 A lot of use of innovative study designs, adaptive designs,

575 00:26:02.940 --> 00:26:03.790 things like that.

576 00:26:05.340 --> 00:26:07.283 Maybe I'll talk a little bit more about that,

577 00:26:08.220 --> 00:26:12.003 and a lot of use with biomarkers and modeling simulation.

578 00:26:13.028 --> 00:26:15.240 If you wanna know more about these sorts of things,

579 00:26:15.240 --> 00:26:18.273 I'll give you a shameless plug for a book.

580 00:26:19.350 --> 00:26:21.360 I'm actually not one of the editors of this book.

581 00:26:21.360 --> 00:26:26.360 These people are my coworkers in our department at Vertex.

582 00:26:27.810 --> 00:26:30.000 I contributed to some of the chapters.

583 00:26:30.000 --> 00:26:32.100 But I think it's a nice book

584 00:26:32.100 --> 00:26:34.893 in that parts of it are technical,

585 00:26:35.910 --> 00:26:37.080 a lot of it isn't,

586 00:26:37.080 --> 00:26:39.360 but it is written by quantitative people

587 00:26:39.360 --> 00:26:42.660 kind of with a quantitative focus on,

588 00:26:42.660 --> 00:26:45.000 or, you know, kind of through a quantitative lens

589 00:26:45.000 --> 00:26:48.150 on what one does and are disease drug development.

590 00:26:48.150 --> 00:26:50.433 So that's my plug.

591 00:26:52.230 --> 00:26:56.280 Little bit of organizational notes about how companies work.

592 00:26:56.280 --> 00:26:59.580 A lot of companies are organized by therapeutic area

593 00:26:59.580 --> 00:27:02.370 and or phase of development.

594 00:27:02.370 --> 00:27:05.340 Some companies have an early phase group

595 00:27:05.340 --> 00:27:07.500 that sort of all they do is phase one studies

596 00:27:07.500 --> 00:27:08.460 and they kinda crank out

597 00:27:08.460 --> 00:27:11.553 these fairly standardized phase one studies.

598 00:27:13.020 --> 00:27:14.640 Vertex is not that way actually,

599 00:27:14.640 --> 00:27:17.460 we just go by different therapeutic areas

600 00:27:17.460 --> 00:27:21.390 and have the same people who do the phase one study

601 00:27:21.390 --> 00:27:23.643 do the phase two, phase three studies.

602 00:27:24.810 --> 00:27:26.520 In general, a lot of companies

603 00:27:26.520 --> 00:27:29.070 are more alike than different.

604 00:27:29.070 --> 00:27:31.370 We have a similar regulatory framework, right?

605 00:27:31.370 --> 00:27:32.677 So like I said, FDA says,

606 00:27:32.677 --> 00:27:34.530 "We want you to do things this way."

607 00:27:34.530 --> 00:27:36.150 So everybody does things that way, right?

608 00:27:36.150 --> 00:27:38.430 We have a lot of the same employees.

609 00:27:38.430 --> 00:27:41.850 So, again, there's different flavors of things, right?

610 00:27:41.850 --> 00:27:43.500 Like the protocol review committee,

611 00:27:43.500 --> 00:27:44.880 they're all gonna have one.

612 00:27:44.880 --> 00:27:46.320 But some companies might have different

613 00:27:46.320 --> 00:27:49.500 protocol review committees for different types of studies,

614 00:27:49.500 --> 00:27:51.757 or maybe it's a little bit different

615 00:27:51.757 --> 00:27:53.790 how they set it up or, you know,

616 00:27:53.790 --> 00:27:55.833 but it's largely the same thing.

617 00:27:57.150 --> 00:27:58.143 For biostats,

618 00:27:59.370 --> 00:28:03.960 my advice would be to inquire with any sort of company

619 00:28:03.960 --> 00:28:06.570 you're thinking about working for or with.

620 00:28:06.570 --> 00:28:08.570 I would inquire about the methods group.

621 00:28:10.890 --> 00:28:12.290 Why do you think I say that?

622 00:28:18.030 --> 00:28:19.140 I'm the methods person,

623 00:28:19.140 --> 00:28:21.180 it's not because the methods group

624 00:28:21.180 --> 00:28:25.620 is the most important group, right?

625 00:28:25.620 --> 00:28:27.020 Why do you think I would say

626 00:28:28.530 --> 00:28:29.940 understand the methods group

627 00:28:29.940 --> 00:28:31.590 at whatever company you might be?

628 00:28:34.890 --> 00:28:37.280 It's actually related to what I just said.

629 00:28:37.280 --> 00:28:41.100 <v ->So maybe to stay on top of the latest trends</v>

630 00:28:41.100 --> 00:28:42.240 in the methods,

631 00:28:42.240 --> 00:28:45.690 make sure that you guys have time devoted for that.

632 00:28:45.690 --> 00:28:46.773 Stay on top of that.

633 00:28:48.568 --> 00:28:50.946 <v ->A very noble answer and kind of right.</v>

634 00:28:50.946 --> 00:28:53.004 (attendant laughing)

635 00:28:53.004 --> 00:28:54.171 I mean kind of

636 00:28:55.040 --> 00:28:59.370 in the sense that how you do that's gonna,

637 00:28:59.370 --> 00:29:02.550 you want to do that, but how you do that is gonna vary.

638 00:29:02.550 --> 00:29:05.130 I just said companies are more similar than different,

639 00:29:05.130 --> 00:29:08.580 but your methods group is an exception to that.

640 00:29:08.580 --> 00:29:10.260 It's actually not standard

641 00:29:10.260 --> 00:29:13.260 and it varies a lot by the company, right?

642 00:29:13.260 --> 00:29:16.530 So I used to work at Novartis, as we told you.

643 00:29:16.530 --> 00:29:21.530 Novartis has pretty much kind of an internal department

644 00:29:21.870 --> 00:29:24.900 of methods that it's almost like a mini academic institution

645 00:29:24.900 --> 00:29:26.250 within the company

646 00:29:26.250 --> 00:29:28.713 that they crank out academic-style papers.

647 00:29:30.540 --> 00:29:34.290 Pretty large group, quite technical in their focus, right?

648 00:29:34.290 --> 00:29:35.190 On the other extreme,

649 00:29:35.190 --> 00:29:36.540 I also used to work for BMS

650 00:29:37.500 --> 00:29:39.930 back when they had a site in Wallingford,

651 00:29:39.930 --> 00:29:41.780 they had no methods group whatsoever.

652 00:29:42.840 --> 00:29:44.550 You wanna do methods? It's your job.

653 00:29:44.550 --> 00:29:46.640 Do it on nights and weekends, whatever, right?

654 00:29:46.640 --> 00:29:48.660 So that's why I mean you're kinda right in the sense that

655 00:29:48.660 --> 00:29:51.247 if you want to do that, you need to understand like,

656 00:29:51.247 --> 00:29:52.740 "Well, am I gonna be working with something

657 00:29:52.740 --> 00:29:53.700 like the Novartis group

658 00:29:53.700 --> 00:29:55.860 or am I doing this all by myself, right?"

659 00:29:55.860 --> 00:29:57.870 So you might ask a board about me.

660 00:29:57.870 --> 00:29:59.940 At Vertex, I'm neither of those

661 00:29:59.940 --> 00:30:01.770 kind of triangulated to that.

662 00:30:01.770 --> 00:30:06.510 I don't have a group. I'm a one man group.

663 00:30:06.510 --> 00:30:10.870 And so I view myself as kind of a facilitator

664 00:30:11.880 --> 00:30:13.740 or a focus kind of person.

665 00:30:13.740 --> 00:30:16.830 So if people are interested in doing methods,

666 00:30:16.830 --> 00:30:18.210 I work with that person.

667 00:30:18.210 --> 00:30:20.220 I'm co-authoring some papers.

668 00:30:20.220 --> 00:30:23.340 I try to keep tabs on things that are going externally,

669 00:30:23.340 --> 00:30:24.180 that kind of thing.

670 00:30:24.180 --> 00:30:29.180 I try to help focus resources and utilize people

671 00:30:29.400 --> 00:30:32.520 who have interest and availability at that time

672 00:30:32.520 --> 00:30:35.343 maybe 'cause they're in that role, you know,

673 00:30:36.509 --> 00:30:39.850 as possible to look at topics

674 00:30:40.889 --> 00:30:42.889 that I can sense are of interest, right?

675 00:30:43.737 --> 00:30:46.230 But my bigger point is it's gonna depend

676 00:30:46.230 --> 00:30:47.790 quite a bit by the company.

677 00:30:47.790 --> 00:30:50.853 FDA's not gonna specify how you use a methods group.

678 00:30:51.750 --> 00:30:54.217 Really quickly, people often ask me,

679 00:30:54.217 --> 00:30:55.680 "Well, what's kinda the difference

680 00:30:55.680 --> 00:30:58.290 between people that are successful and not?"

681 00:30:58.290 --> 00:31:00.030 These are pretty high level, but in general,

682 00:31:00.030 --> 00:31:02.820 communication is important, right?

683 00:31:02.820 --> 00:31:06.690 Being able to make a point concisely, clearly,

684 00:31:06.690 --> 00:31:09.630 being able to communicate with non-statisticians,

685 00:31:09.630 --> 00:31:12.100 being able to give a presentation even in front

686 00:31:13.121 --> 00:31:14.340 of fairly large group of people

687 00:31:14.340 --> 00:31:18.030 and understand and explain your arguments

688 00:31:18.030 --> 00:31:21.300 for why you're doing what you are.

689 00:31:21.300 --> 00:31:23.523 Time management, like I said,

690 00:31:24.600 --> 00:31:27.900 there's a lot going on at a trial, you might be assigned to,

691 00:31:27.900 --> 00:31:30.360 you know, two, three, four, five trials, right?

692 00:31:30.360 --> 00:31:31.650 And they're all at a different point

693 00:31:31.650 --> 00:31:33.150 in that live curve, right?

694 00:31:33.150 --> 00:31:35.970 And so you need to be able to figure out

695 00:31:35.970 --> 00:31:37.380 how you're gonna manage your time

696 00:31:37.380 --> 00:31:39.300 across all those things, right?

697 00:31:39.300 --> 00:31:42.900 So, you know, you're here in school,

698 00:31:42.900 --> 00:31:45.360 maybe you have a job outside, you know,

699 00:31:45.360 --> 00:31:47.666 whatever, at the library, you know?

700 00:31:47.666 --> 00:31:50.490 People here don't care what's going at the library.

701 00:31:50.490 --> 00:31:53.400 Library doesn't care what you're doing here, right?

702 00:31:53.400 --> 00:31:54.930 So you might have five different studies

703 00:31:54.930 --> 00:31:57.660 and you may have to figure out, well,

704 00:31:57.660 --> 00:32:00.270 I need to do this on this study now,

705 00:32:00.270 --> 00:32:02.280 not because the team's telling me they have to,

706 00:32:02.280 --> 00:32:03.480 but because I know next month,

707 00:32:03.480 --> 00:32:05.850 I'm gonna have to do something else in another study.

708 00:32:05.850 --> 00:32:07.800 Right, so you have to kinda like juggle

709 00:32:07.800 --> 00:32:09.240 those different time commitments

710 00:32:09.240 --> 00:32:12.090 and that's something your manager would hopefully be able

711 00:32:12.090 --> 00:32:12.940 to help you with.

712 00:32:13.800 --> 00:32:17.223 But there's some skill in trying to figure that out.

713 00:32:18.120 --> 00:32:20.580 And just being generally proactive and visible.

714 00:32:20.580 --> 00:32:21.603 You want to,

715 00:32:24.670 --> 00:32:25.554 you wanna be seen.

716 00:32:25.554 --> 00:32:27.930 You know, you can give presentations, staff meetings,

717 00:32:27.930 --> 00:32:29.370 there's working groups.

718 00:32:29.370 --> 00:32:30.480 I'm involved with that kinda thing,

719 00:32:30.480 --> 00:32:33.810 which is kind of like a team approach to research, right?

720 00:32:33.810 --> 00:32:35.940 We see a topic that's of interest

721 00:32:35.940 --> 00:32:37.530 and we kinda divvy people up and okay,

722 00:32:37.530 --> 00:32:38.730 well, you can do the simulation,

723 00:32:38.730 --> 00:32:40.530 you go look at the literature.

724 00:32:40.530 --> 00:32:45.011 You know, something to get your name out there

725 00:32:45.011 --> 00:32:45.923 that people can remember you.

726 00:32:47.670 --> 00:32:49.230 But being the methods guy,

727 00:32:49.230 --> 00:32:50.790 I thought I should comment at least a little bit

728 00:32:50.790 --> 00:32:55.443 on some things I see going on in research right now,

729 00:32:56.280 --> 00:32:57.480 what my thoughts on are.

730 00:32:57.480 --> 00:33:00.990 There's a lot going on now with borrowing data

731 00:33:00.990 --> 00:33:02.640 and using real-world data, right?

732 00:33:02.640 --> 00:33:07.020 So people want to do a clinical trial.

733 00:33:07.020 --> 00:33:08.830 It might only be a single-arm study

734 00:33:09.771 --> 00:33:11.190 or it might be randomized,

735 00:33:11.190 --> 00:33:13.560 but they wanna try to use historical data

736 00:33:13.560 --> 00:33:14.970 or real-world data that are out there,

737 00:33:14.970 --> 00:33:18.900 sorta combine the two in a way that borrows strength

738 00:33:18.900 --> 00:33:22.803 and gives you a stronger conclusion.

739 00:33:26.050 --> 00:33:28.620 There's a lot coming out with that now,

740 00:33:28.620 --> 00:33:30.390 there's Bayesian approaches.

741 00:33:30.390 --> 00:33:31.740 I don't know if many of you are familiar

742 00:33:31.740 --> 00:33:34.830 with propensity score, I don't have time to go into it now,

743 00:33:34.830 --> 00:33:37.830 but propensity score is basically an approach for trying

744 00:33:37.830 --> 00:33:42.690 to connect historical data to your clinical trial data

745 00:33:42.690 --> 00:33:46.170 and maybe match patients up in ways

746 00:33:46.170 --> 00:33:47.790 that are similar as possible.

747 00:33:47.790 --> 00:33:50.220 Right, you often know a lot of things the baselines

748 00:33:51.300 --> 00:33:53.640 that are prognostic for the patient, right?

749 00:33:53.640 --> 00:33:56.640 So you try to make it where you're as close

750 00:33:56.640 --> 00:33:59.580 to an apples to apples comparison as possible.

751 00:33:59.580 --> 00:34:02.700 There's a lot of details about exactly how you do that

752 00:34:02.700 --> 00:34:06.000 that I think people can still figure out better

753 00:34:06.000 --> 00:34:07.661 and learn more.

754 00:34:07.661 --> 00:34:09.180 A lot of work with adaptive designs.

755 00:34:09.180 --> 00:34:12.750 For example, you might combine a phase two dose selection

756 00:34:12.750 --> 00:34:14.940 with the phase three efficacy part.

757 00:34:14.940 --> 00:34:19.260 So there's a lot of people looking at that

758 00:34:19.260 --> 00:34:23.310 because you can gain a lot of efficiency by not having to do

759 00:34:23.310 --> 00:34:26.910 a separate phase two study and sort of start all over

760 00:34:26.910 --> 00:34:30.510 with a separate phase three study, right?

761 00:34:30.510 --> 00:34:33.460 My opinion, adaptive designs is that

762 00:34:35.580 --> 00:34:37.673 if you sort of know what you need to do

763 00:34:37.673 --> 00:34:39.960 that is you know your population,

764 00:34:39.960 --> 00:34:41.937 you know what you wanna measure in those people,

765 00:34:41.937 --> 00:34:45.625 you have a decent idea of what your treatment effect may be,

766 00:34:45.625 --> 00:34:47.070 you know, then just do the phase three study

767 00:34:47.070 --> 00:34:48.720 you think you oughta to do, right?

768 00:34:48.720 --> 00:34:50.400 If you're kind of at the other extreme,

769 00:34:50.400 --> 00:34:52.170 you really don't know the answer to much

770 00:34:52.170 --> 00:34:53.370 of any of that stuff,

771 00:34:53.370 --> 00:34:56.280 then you should probably do two separate studies, right?

772 00:34:56.280 --> 00:34:59.100 Just do the phase two study that's not pivotal.

773 00:34:59.100 --> 00:35:00.990 Learn what the heck is going on

774 00:35:00.990 --> 00:35:02.850 and then do the phase three study.

775 00:35:02.850 --> 00:35:05.826 If you're in the middle, which is you kinda mostly know

776 00:35:05.826 --> 00:35:06.659 what you're doing,

777 00:35:06.659 --> 00:35:08.392 but there's this one nagging question,

778 00:35:08.392 --> 00:35:10.800 I don't know if I wanna do the high dose or the low dose,

779 00:35:10.800 --> 00:35:13.560 or I don't know whether the patients need to be, you know,

780 00:35:13.560 --> 00:35:17.220 have this biomarker or maybe a, you know,

781 00:35:17.220 --> 00:35:19.050 I can do it on everybody, you know?

782 00:35:19.050 --> 00:35:19.920 What population?

783 00:35:19.920 --> 00:35:21.480 You have that one nagging question,

784 00:35:21.480 --> 00:35:24.660 that's where an adaptive design can often be helpful, right?

785 00:35:24.660 --> 00:35:29.660 That way, you can build a design around getting information

786 00:35:29.760 --> 00:35:31.950 about that key piece

787 00:35:31.950 --> 00:35:33.993 and going straight into phase three.

788 00:35:35.580 --> 00:35:36.510 A couple things I think

789 00:35:36.510 --> 00:35:38.760 are maybe a little bit under-researched,

790 00:35:38.760 --> 00:35:40.263 could be looked at more.

791 00:35:41.430 --> 00:35:43.920 I think a single-arm design that can change

792 00:35:43.920 --> 00:35:46.020 to a randomized design, stage two,

793 00:35:46.020 --> 00:35:50.010 is something I would like to see a better treatment of

794 00:35:50.010 --> 00:35:52.398 because what I was talking about before

795 00:35:52.398 --> 00:35:53.400 with the real-world data,

796 00:35:53.400 --> 00:35:55.470 you're trying to compare it, right?

797 00:35:55.470 --> 00:35:58.440 That works best in the extreme cases, right?

798 00:35:58.440 --> 00:36:02.460 So if the real-world data say this is what happens

799 00:36:02.460 --> 00:36:04.080 to an untreated patient, right?

800 00:36:04.080 --> 00:36:05.970 You tend to see this sort of result.

801 00:36:05.970 --> 00:36:09.720 If you do a single-arm study in your experimental therapy

802 00:36:09.720 --> 00:36:12.810 and it looks the same, then you have a good answer.

803 00:36:12.810 --> 00:36:15.203 The answer is your drug's not that good

804 00:36:15.203 --> 00:36:17.580 and, you know, and you've done it efficiently, right?

805 00:36:17.580 --> 00:36:19.470 Single-arm study is smaller, right?

806 00:36:19.470 --> 00:36:22.500 If the results are great, much better,

807 00:36:22.500 --> 00:36:24.660 then you've also have a good answer, right?

808 00:36:24.660 --> 00:36:27.450 Even if there's some bias in the real-world data,

809 00:36:27.450 --> 00:36:28.953 the results are so big,

810 00:36:30.030 --> 00:36:31.740 it's gotta be something good with the drug

811 00:36:31.740 --> 00:36:33.390 going on there, right?

812 00:36:33.390 --> 00:36:36.330 It's that middle case that's kind of awkward, right?

813 00:36:36.330 --> 00:36:39.987 Well, it's better, but it's maybe even p is less than 0.05,

814 00:36:39.987 --> 00:36:42.300 but there might be bias in that historical data

815 00:36:42.300 --> 00:36:44.970 and dang, I wish I'd done a randomized study

816 00:36:44.970 --> 00:36:46.770 sometimes what you might think, right?

817 00:36:46.770 --> 00:36:48.750 So then I think it'd be interesting,

818 00:36:48.750 --> 00:36:50.580 you do state choose the randomized study,

819 00:36:50.580 --> 00:36:53.280 you combine the two phases, right?

820 00:36:53.280 --> 00:36:56.820 And then you come up with one result for the whole study.

821 00:36:56.820 --> 00:36:58.710 And lastly, I'll mention,

822 00:36:58.710 --> 00:37:00.240 I think there's more actually to do

823 00:37:00.240 --> 00:37:01.690 with good old stratification.

824 00:37:04.440 --> 00:37:07.230 We've had a couple situations where we were unsure

825 00:37:07.230 --> 00:37:09.270 how to stratify in a study.

826 00:37:09.270 --> 00:37:11.700 We actually had a group go back, look at the literature,

827 00:37:11.700 --> 00:37:15.840 the literature actually a little bit more thin,

828 00:37:15.840 --> 00:37:19.440 vague and conservative than I thought it was.

829 00:37:19.440 --> 00:37:22.290 If you really want to understand, hey, from my study,

830 00:37:22.290 --> 00:37:24.843 I've got 150 patients, these are the factors.

831 00:37:26.220 --> 00:37:28.620 It not actually specific as you might think.

832 00:37:28.620 --> 00:37:30.630 And you can get into things like whether

833 00:37:30.630 --> 00:37:33.210 the stratification factors are correlated

834 00:37:33.210 --> 00:37:35.043 with each other, right?

835 00:37:36.090 --> 00:37:39.240 And continuous factors you might wanna stratify on

836 00:37:39.240 --> 00:37:41.040 is another kinda area people could go.

837 00:37:41.040 --> 00:37:43.860 So I think there's still more to do there.

838 00:37:43.860 --> 00:37:46.080 I say it's important for small studies, right?

839 00:37:46.080 --> 00:37:47.820 So if you're doing a big study,

840 00:37:47.820 --> 00:37:49.740 the law of large numbers is gonna probably cover,

841 00:37:49.740 --> 00:37:52.057 you could probably stratify nothing

842 00:37:52.057 --> 00:37:53.760 and it'll be probably okay, right?

843 00:37:53.760 --> 00:37:56.490 But studies are getting smaller and smaller,

844 00:37:56.490 --> 00:37:58.770 people are in more and more focused groups.

845 00:37:58.770 --> 00:38:00.630 A small study,

846 00:38:00.630 --> 00:38:03.720 if I can say something a little bit controversial,

847 00:38:03.720 --> 00:38:07.383 small randomized studies I think are a bit dangerous, right?

848 00:38:08.370 --> 00:38:11.130 People love this notion that a randomized study's unbiased,

849 00:38:11.130 --> 00:38:13.533 but that's in the long term.

850 00:38:14.790 --> 00:38:17.280 I only get one chance to do my study.

851 00:38:17.280 --> 00:38:19.860 There's only 30 or 40 patients in it

852 00:38:19.860 --> 00:38:21.330 that might not be big enough to guarantee

853 00:38:21.330 --> 00:38:22.710 that everything's gonna work out even.

854 00:38:22.710 --> 00:38:24.870 So that could be a little bit dangerous.

855 00:38:24.870 --> 00:38:26.070 If you're gonna do it,

856 00:38:26.070 --> 00:38:28.170 you might wanna think about stratification carefully.

857 00:38:28.170 --> 00:38:29.889 Probably already talked to you.

858 00:38:29.889 --> 00:38:31.145 I wanted to leave at least eight minutes.

859 00:38:31.145 --> 00:38:32.571 <v ->Okay, you've got plenty of time,</v>

860 00:38:32.571 --> 00:38:33.690 you've got like 10 minutes.

861 00:38:33.690 --> 00:38:36.613 <v ->I think I was told like or by 12:50 or whatever.</v>

862 00:38:38.131 --> 00:38:40.030 <v ->Yeah, we have to be done by 12:50, yeah.</v>

863 00:38:40.030 --> 00:38:41.708 By 12:50. <v ->Right, so.</v>

864 00:38:41.708 --> 00:38:44.697 <v ->Question.</v> <v ->12:40, so we got like 10.</v>

865 00:38:44.697 --> 00:38:46.438 <v ->Anyone in the room or on.</v>

866 00:38:46.438 --> 00:38:47.744 <v ->Yes.</v>

867 00:38:47.744 --> 00:38:49.380 <v ->So, okay, I feel like drug development,</v>

868 00:38:49.380 --> 00:38:51.510 and in particular FDA, are pretty conservative

869 00:38:51.510 --> 00:38:53.010 with how they like designed their trials,

870 00:38:53.010 --> 00:38:55.260 especially with like phase two and phase three trials.

871 00:38:55.260 --> 00:38:56.400 So again,

872 00:38:56.400 --> 00:38:57.660 obviously, you've talking about like some of these

873 00:38:57.660 --> 00:39:00.780 more interesting like, you know, ideas like adaptive trials.

874 00:39:00.780 --> 00:39:03.300 And let's say like you're in a company that like has,

875 00:39:03.300 --> 00:39:06.600 I'm not sure Vertex has done a kind of adaptive trial,

876 00:39:06.600 --> 00:39:07.680 not that I'm aware of.

877 00:39:07.680 --> 00:39:09.780 But like if let's say

878 00:39:09.780 --> 00:39:11.400 you thought it's a good idea for a certain drug,

879 00:39:11.400 --> 00:39:13.590 for a certain program, like how would you go about

880 00:39:13.590 --> 00:39:17.160 like making the case that an adaptive trial is better?

881 00:39:17.160 --> 00:39:18.810 Like obviously, like this is assuming

882 00:39:18.810 --> 00:39:20.430 you have like a theory behind it

883 00:39:20.430 --> 00:39:22.230 that it is, for some reason, better.

884 00:39:23.310 --> 00:39:27.030 <v ->Yeah, that's a very good question.</v>

885 00:39:27.030 --> 00:39:28.530 We do have an adaptive study actually,

886 00:39:28.530 --> 00:39:29.940 the one like I had mentioned there

887 00:39:29.940 --> 00:39:32.850 with two different doses, do a phase two,

888 00:39:32.850 --> 00:39:36.630 and then we're gonna pick a dose and dose into phase three.

889 00:39:36.630 --> 00:39:38.910 There's a series of meetings.

890 00:39:38.910 --> 00:39:42.240 I didn't have time to talk about it,

891 00:39:42.240 --> 00:39:44.670 but there's like type A, type B, type C meetings

892 00:39:44.670 --> 00:39:47.040 you have with FDA along the way.

893 00:39:47.040 --> 00:39:48.330 There's another type of meeting,

894 00:39:48.330 --> 00:39:50.850 one of them is called the end of phase two meeting.

895 00:39:50.850 --> 00:39:52.320 So you do have meetings at FDA

896 00:39:52.320 --> 00:39:54.397 where you can propose things and say,

897 00:39:54.397 --> 00:39:56.787 "Hey, we think we oughta do it this way."

898 00:39:58.410 --> 00:40:00.600 As you may have briefly seen on the slide

899 00:40:00.600 --> 00:40:01.953 about rare diseases,

900 00:40:02.910 --> 00:40:06.573 the regulatory framework on rare diseases is less certain,

901 00:40:07.560 --> 00:40:09.150 which is both good and bad.

902 00:40:09.150 --> 00:40:12.900 I mean, right, it can be bad in the sense

903 00:40:12.900 --> 00:40:16.170 that you're not really sure what you're allowed to do.

904 00:40:16.170 --> 00:40:17.370 But it's also good in the sense

905 00:40:17.370 --> 00:40:20.107 that it's more possible for you to argue things like,

906 00:40:20.107 --> 00:40:23.790 "Hey, there's not that many, you know,

907 00:40:23.790 --> 00:40:26.610 say kids with Duchenne muscular dystrophy, you know?"

908 00:40:26.610 --> 00:40:28.290 It's not that big a population.

909 00:40:28.290 --> 00:40:29.990 These kids have a serious disease.

910 00:40:31.080 --> 00:40:32.970 We need some flexibility in our design

911 00:40:32.970 --> 00:40:35.430 to show that our drug is working, you know?

912 00:40:35.430 --> 00:40:37.893 So it's a little bit easier in rare diseases.

913 00:40:38.730 --> 00:40:39.660 So you could either use

914 00:40:39.660 --> 00:40:42.150 those type A, B, C meetings with them

915 00:40:42.150 --> 00:40:43.890 and, of course, you're gonna send them

916 00:40:43.890 --> 00:40:45.570 your protocol and stuff

917 00:40:45.570 --> 00:40:48.210 to sort of make your case in a meeting.

918 00:40:48.210 --> 00:40:50.280 They also have a program called

919 00:40:50.280 --> 00:40:52.980 the Complex Innovative Design Program,

920 00:40:52.980 --> 00:40:55.860 which is actually run by their stats people

921 00:40:55.860 --> 00:40:58.360 where you can set up extra meetings

922 00:40:59.370 --> 00:41:01.980 to review things like simulations, right?

923 00:41:01.980 --> 00:41:06.780 So their biggest concern is maintaining type one error,

924 00:41:06.780 --> 00:41:08.280 right? <v ->So I mean like,</v>

925 00:41:08.280 --> 00:41:10.410 so I worked in drug development for the past six years

926 00:41:10.410 --> 00:41:14.340 and like interacting with FDA and like FDA minutes and such,

927 00:41:14.340 --> 00:41:16.740 like I've seen like them like say one thing

928 00:41:16.740 --> 00:41:17.573 and then like the next meeting say,

929 00:41:17.573 --> 00:41:19.590 "Actually, we change our minds."

930 00:41:19.590 --> 00:41:21.660 Or they give like vague answers.

931 00:41:21.660 --> 00:41:23.730 And so you like internally have to kinda figure out

932 00:41:23.730 --> 00:41:25.167 like what you're gonna do.

933 00:41:25.167 --> 00:41:26.000 So like in those situations,

934 00:41:26.000 --> 00:41:27.960 like where okay, like FDA like might be okay,

935 00:41:27.960 --> 00:41:29.670 we're not actually sure, like I guess

936 00:41:29.670 --> 00:41:31.650 like how do you build like the,

937 00:41:31.650 --> 00:41:33.060 and then obviously, the tendency then

938 00:41:33.060 --> 00:41:34.960 is to like just go back into just do

939 00:41:35.849 --> 00:41:36.682 like just what you traditionally done,

940 00:41:36.682 --> 00:41:37.920 but like if you like are really advocating

941 00:41:37.920 --> 00:41:39.990 for something like this.

942 00:41:39.990 --> 00:41:41.220 <v ->Yeah, there's a balance there.</v>

943 00:41:41.220 --> 00:41:42.053 It's not uncommon

944 00:41:42.053 --> 00:41:44.670 to be like not completely sure what FDA does.

945 00:41:44.670 --> 00:41:48.480 I mean if you schedule one of these meetings with 'em,

946 00:41:48.480 --> 00:41:50.370 yeah, they will give you a response.

947 00:41:50.370 --> 00:41:52.620 It might be in person, it might be written,

948 00:41:52.620 --> 00:41:55.590 it might not be everything you would want to see.

949 00:41:55.590 --> 00:41:57.510 You might still have questions after seeing it.

950 00:41:57.510 --> 00:41:59.070 So it depends.

951 00:41:59.070 --> 00:42:00.690 Sometimes they're pretty clear,

952 00:42:00.690 --> 00:42:03.120 no, we don't like this or whatever.

953 00:42:03.120 --> 00:42:04.470 Other times, you're kinda still

954 00:42:04.470 --> 00:42:06.120 kinda scratching your head a bit.

955 00:42:07.170 --> 00:42:09.780 A lot of times, they say something is a review issue,

956 00:42:09.780 --> 00:42:11.750 which means, well, you know,

957 00:42:11.750 --> 00:42:13.560 if you get the data, we'll look at it

958 00:42:13.560 --> 00:42:14.710 and see then, you know?

959 00:42:16.830 --> 00:42:18.720 So that's kinda the best you can do.

960 00:42:18.720 --> 00:42:20.550 It's difficult to get certainty.

961 00:42:20.550 --> 00:42:23.100 There's definitely a lot of planning

962 00:42:23.100 --> 00:42:24.933 around communication with FDA.

963 00:42:26.010 --> 00:42:26.970 What do we wanna say?

964 00:42:26.970 --> 00:42:28.110 I think of it a little bit

965 00:42:28.110 --> 00:42:31.500 as kinda like going to the oracle in ancient Greece, right?

966 00:42:31.500 --> 00:42:33.660 It's sort of like, you know,

967 00:42:33.660 --> 00:42:36.259 you have to plan and hope that, you know,

968 00:42:36.259 --> 00:42:37.530 they're gonna tell you.

969 00:42:37.530 --> 00:42:41.400 You can interpret what sort of prophetic thing

970 00:42:41.400 --> 00:42:42.753 they're going to tell you.

971 00:42:44.160 --> 00:42:46.530 Sorry, I don't have a better answer for you than that.

972 00:42:46.530 --> 00:42:49.050 Oh, but what I was saying earlier was there is something

973 00:42:49.050 --> 00:42:51.840 called the Complex Innovative Design Program

974 00:42:51.840 --> 00:42:54.600 where you can set up,

975 00:42:54.600 --> 00:42:58.440 if they accept you, you get like two extra meetings

976 00:42:58.440 --> 00:43:00.120 where you can review things like simulations.

977 00:43:00.120 --> 00:43:03.427 So if you wanna do something complicated, they'll often say,

978 00:43:03.427 --> 00:43:07.050 "Well, we wanna make sure type one error is controlled."

979 00:43:07.050 --> 00:43:09.157 And if the answer to that question is,

980 00:43:09.157 --> 00:43:12.390 "Well, we got a bunch of simulations to show you

981 00:43:12.390 --> 00:43:14.190 that it controls type one error,"

982 00:43:14.190 --> 00:43:16.380 then you might wanna do something like that

983 00:43:16.380 --> 00:43:18.630 to kinda dig through the details of,

984 00:43:18.630 --> 00:43:21.380 well, how did you set up your simulations and all that.

985 00:43:23.430 --> 00:43:24.263 Other questions?

986 00:43:26.747 --> 00:43:29.630 I feel like I've been ignoring everybody over here.

987 00:43:29.630 --> 00:43:30.510 <v ->Got a question over here.</v>

988 00:43:30.510 --> 00:43:32.010 <v ->Oh, yes.</v>

989 00:43:32.010 --> 00:43:34.514 <v Student>Thank you for the presentation.</v>

990 00:43:34.514 --> 00:43:35.610 The question is,

991 00:43:35.610 --> 00:43:38.250 is it possible to revise your SAP

992 00:43:38.250 --> 00:43:39.810 after the trial started?

993 00:43:39.810 --> 00:43:43.713 If the answer is yes, is there any restriction on it?

994 00:43:45.900 --> 00:43:50.160 <v ->So again, back to the blinded versus unblinded, right?</v>

995 00:43:50.160 --> 00:43:53.760 If it's an unblinded study, you can,

996 00:43:53.760 --> 00:43:56.820 but it's gonna be viewed suspiciously,

997 00:43:56.820 --> 00:43:58.320 for lack of a better word, right?

998 00:43:58.320 --> 00:44:01.170 It's gonna be viewed as a post hoc change.

999 00:44:01.170 --> 00:44:02.520 Why are you changing this?

1000 00:44:02.520 --> 00:44:03.970 You suspected that something,

1001 00:44:04.890 --> 00:44:06.993 if it's a blinded study, yes, you can.

1002 00:44:08.040 --> 00:44:10.890 You can amend your SAP.

1003 00:44:10.890 --> 00:44:12.960 That's not terribly uncommon.

1004 00:44:12.960 --> 00:44:14.040 For example, you might,

1005 00:44:14.040 --> 00:44:16.770 during the course of the study, still blinded,

1006 00:44:16.770 --> 00:44:18.960 you might learn new information,

1007 00:44:18.960 --> 00:44:20.790 new published data may come out.

1008 00:44:20.790 --> 00:44:23.730 You might learn something about the baseline data

1009 00:44:23.730 --> 00:44:25.830 on your study, you know, the distribution

1010 00:44:25.830 --> 00:44:26.980 or something like that.

1011 00:44:27.990 --> 00:44:32.310 So as a result, you may wanna pivot what your SAP is

1012 00:44:32.310 --> 00:44:34.110 and if it's still blinded,

1013 00:44:34.110 --> 00:44:36.570 generally speaking, you could still do that

1014 00:44:36.570 --> 00:44:38.343 and it'd be used pre-specified.

1015 00:44:39.360 --> 00:44:40.193 <v Student>Thank you.</v>

1016 00:44:42.300 --> 00:44:43.950 <v ->Yes.</v>

1017 00:44:43.950 --> 00:44:45.570 <v Learner>I'm very sure that there should be</v>

1018 00:44:45.570 --> 00:44:48.450 many variables to consider when it comes to this study.

1019 00:44:48.450 --> 00:44:52.080 And in case of these small sample size studies,

1020 00:44:52.080 --> 00:44:54.240 I'm pretty sure that a stratification

1021 00:44:54.240 --> 00:44:57.360 might really be inefficient

1022 00:44:57.360 --> 00:45:00.810 to contain all these variables at one place.

1023 00:45:00.810 --> 00:45:02.130 And I'm very curious,

1024 00:45:02.130 --> 00:45:05.010 how do you actually like manage when it comes

1025 00:45:05.010 --> 00:45:06.350 to the small sample size

1026 00:45:06.350 --> 00:45:07.183 studies? <v ->Yeah.</v>

1027 00:45:07.183 --> 00:45:08.310 Yeah, also good question.

1028 00:45:08.310 --> 00:45:11.280 Again, I think this is a good area for more research.

1029 00:45:11.280 --> 00:45:13.473 We had a group look at some simulations.

1030 00:45:14.654 --> 00:45:17.730 Here's my qualitative assessment of what we found.

1031 00:45:17.730 --> 00:45:20.970 One, I think in general, people worry a bit too much

1032 00:45:20.970 --> 00:45:22.220 about what you're saying.

1033 00:45:23.310 --> 00:45:26.880 As long as like the marginals work out pretty well,

1034 00:45:26.880 --> 00:45:29.790 then you're actually probably still okay

1035 00:45:29.790 --> 00:45:31.683 as far as stratification goes.

1036 00:45:33.570 --> 00:45:37.353 I think there's a bigger danger of bad luck imbalance.

1037 00:45:39.120 --> 00:45:40.800 I don't wanna speculate too much,

1038 00:45:40.800 --> 00:45:44.040 but there was a competitor that had a study come out,

1039 00:45:44.040 --> 00:45:46.470 rare disease, small study,

1040 00:45:46.470 --> 00:45:48.540 just by bad luck, they had some imbalance

1041 00:45:48.540 --> 00:45:50.220 in one other strata.

1042 00:45:50.220 --> 00:45:55.110 And maybe it could be the reason why the study,

1043 00:45:55.110 --> 00:45:56.793 statistically speaking, failed.

1044 00:45:58.590 --> 00:46:03.590 And so, yeah, here's my sports analogy, okay?

1045 00:46:04.020 --> 00:46:07.500 So small studies are kind of like a football game

1046 00:46:07.500 --> 00:46:09.723 where you're losing at the end of the game.

1047 00:46:10.920 --> 00:46:13.920 You wanna throw the ball 'cause you need to score, right?

1048 00:46:13.920 --> 00:46:16.560 The defense is going to be playing for that.

1049 00:46:16.560 --> 00:46:18.450 They're gonna make it harder for you to do that,

1050 00:46:18.450 --> 00:46:20.580 but you need to do it anyhow, right?

1051 00:46:20.580 --> 00:46:22.290 That's kinda like the way stratification is.

1052 00:46:22.290 --> 00:46:24.600 Yes, it's harder to do it in a small study,

1053 00:46:24.600 --> 00:46:27.690 but you need to think about it and try to do it anyhow.

1054 00:46:27.690 --> 00:46:29.317 'Cause if you just throw your hands up and say,

1055 00:46:29.317 --> 00:46:32.580 "Eh, whatever," then you might have what happened to you,

1056 00:46:32.580 --> 00:46:34.230 what happened to this competitor.

1057 00:46:35.760 --> 00:46:39.240 And so we actually wrote a program so you could simulate

1058 00:46:39.240 --> 00:46:42.450 and say, "Hey, from my study, I've got X patients,

1059 00:46:42.450 --> 00:46:45.180 these are the stratification factors.

1060 00:46:45.180 --> 00:46:47.930 What's gonna happen to my type one and type two error?"

1061 00:46:48.844 --> 00:46:50.790 But you are right that in principle,

1062 00:46:50.790 --> 00:46:51.903 you can't overdo it.

1063 00:46:52.800 --> 00:46:54.480 I just think the point where you overdo it

1064 00:46:54.480 --> 00:46:57.483 is further out than most people think.

1065 00:47:01.860 --> 00:47:02.853 <v ->Two more minutes.</v>

1066 00:47:03.810 --> 00:47:04.893 Any other questions?

1067 00:47:07.830 --> 00:47:08.673 Or online?

1068 00:47:10.590 --> 00:47:13.056 <v ->Sorry if I've ignored people online.</v>

1069 00:47:13.056 --> 00:47:13.889 <v ->We have-</v>

1070 00:47:13.889 --> 00:47:14.981 <v Student>I have a question.</v>

1071 00:47:14.981 --> 00:47:17.475 <v ->I don't know how many people we have online.</v>

1072 00:47:17.475 --> 00:47:19.086 <v ->Let me just move to see if there's the chat.</v>

1073 00:47:19.086 --> 00:47:19.919 <v ->Do I?</v>

1074 00:47:21.091 --> 00:47:21.924 <v ->To pop up.</v>

1075 00:47:21.924 --> 00:47:23.733 <v ->Oh, it would pop up? Okay.</v>

1076 00:47:24.720 --> 00:47:26.787 That's doesn't look like we have any chat.

1077 00:47:26.787 --> 00:47:28.443 <v Student>Can I ask a question?</v>

1078 00:47:29.310 --> 00:47:31.290 So you mentioned time management

1079 00:47:31.290 --> 00:47:34.203 as an important skill obviously.

1080 00:47:35.400 --> 00:47:37.250 Can you tell us about sort of what is

1081 00:47:39.050 --> 00:47:42.030 the work cycle of a biostatistician?

1082 00:47:42.030 --> 00:47:46.470 So are they working on many studies at one time?

1083 00:47:46.470 --> 00:47:50.490 Are they getting a lot of experience doing phase one

1084 00:47:50.490 --> 00:47:54.693 or what's the volume of which they're working on and how?

1085 00:47:55.950 --> 00:47:59.370 <v ->Yeah, it's, as you expect it, you know, it depends.</v>

1086 00:47:59.370 --> 00:48:02.620 I mean what sort of study someone has assigned to you

1087 00:48:03.780 --> 00:48:05.070 is a little bit random.

1088 00:48:05.070 --> 00:48:07.680 I mean what they need somebody to do.

1089 00:48:07.680 --> 00:48:11.130 It's not uncommon for people to be assigned to say

1090 00:48:11.130 --> 00:48:16.080 two to five studies depending on how big they are,

1091 00:48:16.080 --> 00:48:19.113 how short you are on people, et cetera, you know?

1092 00:48:20.340 --> 00:48:22.710 And so you have to try and manage that kind of work.

1093 00:48:22.710 --> 00:48:25.470 I was just talking about across those, you know,

1094 00:48:25.470 --> 00:48:27.630 say two to five studies.

1095 00:48:27.630 --> 00:48:32.630 You also spend, I'd say roughly 10 to 20% of your time

1096 00:48:34.350 --> 00:48:36.780 doing non-project stuff.

1097 00:48:36.780 --> 00:48:40.050 Things I mentioned like the working groups,

1098 00:48:40.050 --> 00:48:41.670 maybe some independent research,

1099 00:48:41.670 --> 00:48:43.950 maybe other kinda service to the department.

1100 00:48:43.950 --> 00:48:45.150 I mean, you know, obviously,

1101 00:48:45.150 --> 00:48:47.650 I spend time interviewing people, stuff like that.

1102 00:48:48.570 --> 00:48:53.040 So that's kind of the breakdown of what people are doing.

1103 00:48:53.040 --> 00:48:54.510 <v Student>And are they working in teams</v>

1104 00:48:54.510 --> 00:48:56.370 as statisticians or?

1105 00:48:56.370 --> 00:48:58.680 <v ->Yeah, so you would have, you know, again,</v>

1106 00:48:58.680 --> 00:49:00.600 you have a project level, right?

1107 00:49:00.600 --> 00:49:02.400 So you would have a project statistician,

1108 00:49:02.400 --> 00:49:04.803 somebody who's somewhat more senior,

1109 00:49:05.880 --> 00:49:07.740 who manages the whole project.

1110 00:49:07.740 --> 00:49:10.590 And then under that person, you might have whatever,

1111 00:49:10.590 --> 00:49:12.210 you know, two, three, four,

1112 00:49:12.210 --> 00:49:14.490 depends how big the project is,

1113 00:49:14.490 --> 00:49:17.280 statisticians who manage individual studies, right?

1114 00:49:17.280 --> 00:49:19.440 So you might have, you know, I don't know,

1115 00:49:19.440 --> 00:49:21.027 10 studies in the project, right?

1116 00:49:21.027 --> 00:49:23.640 And you might have three statisticians

1117 00:49:23.640 --> 00:49:27.030 who each have three each or something like that

1118 00:49:27.030 --> 00:49:29.040 reporting to that project statistician

1119 00:49:29.040 --> 00:49:33.363 who's kinda doing the overall work on the drug.

1120 00:49:35.940 --> 00:49:37.050 <v ->All right.</v>

1121 00:49:37.050 --> 00:49:40.203 So thanks so much.

1122 00:49:41.250 --> 00:49:42.390 In the interest of time,

1123 00:49:42.390 --> 00:49:44.460 we're going to go ahead and stop here.

1124 00:49:44.460 --> 00:49:46.160 But let's thank our speaker again.

1125 00:49:50.070 --> 00:49:51.850 <v ->Great insight into the industry</v>

1126 00:49:53.850 --> 00:49:56.580 and have a wonderful day.

1127 00:49:56.580 --> 00:49:57.413 <v ->Sign in sheet.</v>

1128 00:49:57.413 --> 00:49:58.246 <v ->Oh yeah.</v>

1129 00:49:58.246 --> 00:49:59.550 We have a sign in sheet.

1130 00:49:59.550 --> 00:50:02.068 (attendants chattering indistinctly)

1131 00:50:02.068 --> 00:50:02.901 Thank you.

1132 00:50:02.901 --> 00:50:07.318 (attendants chattering indistinctly)

1133 00:50:09.890 --> 00:50:12.783 So we got a couple of 'em up here.

1134 00:50:14.520 --> 00:50:16.370 You still need to sign in, please do.

1135 00:50:17.265 --> 00:50:18.098 <v ->The thing is that</v>

1136 00:50:18.098 --> 00:50:19.349 (student muttering indistinctly)

1137 00:50:19.349 --> 00:50:21.973 well, technically, have like four, five.

1138 00:50:21.973 --> 00:50:23.856 (students chattering indistinctly)