Table 4: Framework of Approaches for Safety Monitoring and Managing Safety Signals when using Digital Health Technologies for Data Capture

This framework is intended to be used as a tool supporting sponsors seeking to optimize their approach for managing atypical data, including those data captured outside of the intended use of the digital technology. Here CTTI defines a variety of options for addressing unanticipated data, describes the implications and applications of these options, and provides illustrative examples of how these approaches may be applied in practice. For additional considerations pertaining to handling safety signals, please reference CTTI Recommendations for Managing Data.

Technology/Data Capability	Approach	Implications & Applications	Illustrative Examples	
The digital technology is not intended for safety monitoring.	Participants are educated at enrollment, through the informed consent process, that the digital technology is not intended for adverse event monitoring and that they should not depend on it for such. Any adverse events should be reported to the investigator through the usual channels.	Researchers do not have an obligation to analyze data for an endpoint that is not in line with the intended use of the digital technology. With this approach, participants should be informed at enrollment that the technology is not providing any safety monitoring. CTTI recommends that participants be reminded of this throughout the trial. This approach is one option that may be considered when the digital technology does not provide data that could reliably be interpreted as a safety signal in the context of use of the study.	**Intended use:** Actimetry sensor captures data that is processed to generate information on movement that is known to be accurate and reliable in the context of a post-op study of knee replacement patients. The outcome of interest that the digital technology will be measuring include physical activity outcomes such as steps and time in moderate-to-vigorous physical activity (MVPA). **Safety monitoring:** While an actimetry sensor could conceivably provide an indication if a patient falls, the data captured has not been validated for this measure. Therefore, with this approach, the data would not be analyzed to detect falls. The absence of safety monitoring by the digital technology should be clearly communicated during the informed consent process.	**Intended use:** Cardiac monitor captures and processes data that accurately and reliably detects episodes of atrial fibrillation in high risk patients. This is the efficacy endpoint that the digital technology will be collecting. **Safety monitoring:** While a cardiac monitor could feasibly detect other cardiac events, if the data captured and processing applied to it has not been validated for these measures, applying this approach dictates that monitoring the data through the application of non-validated algorithms is not necessary. The absence of safety monitoring should be clearly communicated during the informed consent process.
The digital technology is not intended for safety monitoring.	Participants are educated at enrollment, through the informed consent process, that the digital technology is not intended for safety and that they should not depend on it for such. Participants are also told that if any results that	This approach would provide the option of analyzing data generated for safety endpoints (either at the individual patient level or aggregate level) that fall out of scope of the intended use of the digital technology. This approach may be considered when there is no validated precedence of the use of the data for a specific safety endpoint but there is interest in undertaking a methodological study to explore feasibility of achieving this. (Click	**Intended use:** Actimetry sensor captures data that is processed to generate information on movement that is known to be accurate and reliable in the context of a post-op study of knee replacement patients. The outcome of interest that the digital technology will be measuring include physical activity outcomes such as steps and time in moderate-to-vigorous physical activity (MVPA). **Safety monitoring:** If an exploratory algorithm	**Intended use:** Cardiac monitor captures and processes data that accurately and reliably detects episodes of atrial fibrillation in high risk patients. This is the efficacy endpoint that the digital technology will be collecting. The technology is also capable of accurately and reliably detecting heart rhythm abnormalities known to signal cardiac arrest or heart attack. **Safety monitoring:** If an exploratory

	may indicate a safety concern are detected in their data, these will be discussed with them.	here for CTTI considerations on developing technology derived novel endpoints). To ensure that further interrogation is valuable, this approach would require planning to capture the appropriate level of information in the protocol, i.e. sampling approaches and meta-data.	for detecting patient falls using data from this sensor exists, applying this approach prescribes that the data is monitored for suspected falls and that an SOP for further interrogation of suspected falls should be applied where appropriate. Since the algorithm is only exploratory, the absence of safety monitoring should be clearly communicated during the informed consent process.	algorithm for detecting other cardiac events—such as cardiac arrest or heart attack—from this sensor exists, applying this approach prescribes that the data is monitored for suspected cardiac events and that an SOP for further interrogation of suspected cardiac events should be applied where appropriate. Since the algorithm is only exploratory, the absence of safety monitoring should be clearly communicated during the informed consent process.
The digital technology selected is capable of accurately and reliably measuring pre-specified, valid safety measure(s) in the context of use of the trial.	Action(s) to be taken following the detection of a safety signal or adverse event by a digital technology should be pre-specified in the protocol and clearly communicated to participants.	This approach requires that the pre-specified safety measures are valid in the context of use of the trial. Also, that the digital technology selected is capable of accurately and reliably assessing this measure. This approach will likely also require additional monitoring of data from the technology. (Click here for CTTI considerations on study monitoring when using digital technologies for data capture). CTTI recommends that study participants be included in decision making on how to handle responses to safety signals and adverse events detected remotely by digital technologies. Specifically, to whom this information may be communicated beyond the study investigator and required safety reporting. Also, what, if any, immediate action will be taken in response to safety events detected in real time.	**Intended use:** Actimetry sensor captures data that is processed to generate information on movement that is known to be accurate and reliable in the context of a post-op study of knee replacement patients. The outcome of interest that the digital technology will be measuring is range of motion of the knee. The technology is also capable of accurately and reliably detecting falls in this context of use. **Safety monitoring:** The data should be monitored for atypical data indicating that participant may have fallen. If such data is observed, a pre-specified SOP for handling such information should be followed.	**Intended use:** Cardiac monitor captures and processes data that accurately and reliably detects episodes of atrial fibrillation in high risk patients. This is the efficacy endpoint that the digital technology will be collecting. The technology is also capable of accurately and reliably detecting heart rhythm abnormalities known to signal cardiac arrest or heart attack. **Safety monitoring:** The data should be monitored for atypical data indicating a possible cardiac arrest or heart attack. If such data is observed, a pre-specified SOP for handling such information should be followed.

This framework has been adapted from framework developed by Bora & Sorenson[*] and Illes et al.[†] describing options for handling incidental findings during clinical research using MRI scans.

[*] Borra, Ronald JH, and A. Gregory Sorensen. "Incidental findings in brain MRI research: what do we owe our subjects?." *Journal of the American College of Radiology* 8.12 (2011): 848-852.
[†] Illes, Judy, et al. "Practical approaches to incidental findings in brain imaging research." *Neurology* 70.5 (2008): 384-390.